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Volume 236 APRIL 24, 1947 Number 17

STREPTOMYCIN TREATMENT OF PULMONARY INFECTIONS*

Clinical and Bacteriologic Studies of Six Cases

H. WILLIAM HARRIS, M.D.,† RODERICK MURRAY, M.D.,‡ TOM F. PAINE, M.D.,§ AND MAXWELL FINLAND, M.D.¶

BOSTON

ALTHOUGH pulmonary infections caused by gram-negative bacilli are much less frequent than those caused by gram-positive cocci, they are generally severe and often leave serious damage in the lungs of patients who recover. Their importance has become particularly evident since the advent of the sulfonamides and penicillin, which have produced highly favorable results in pneumococcal, streptococcal and staphylococcal pneumonias but have not materially influenced those due to gram-negative bacilli.

Since the original report by Schatz, Bugie and Waksman[1] on streptomycin and its antibacterial action against certain gram-negative bacilli, numerous studies have confirmed the marked effect of this antibiotic against most gram-negative bacteria including those that cause pulmonary infections.[2–7] There are few reports, however, on the clinical use of streptomycin in pulmonary infections. Herrell and Nichols[8] treated 5 cases of suppurative disease of the tracheobronchial tree caused by a variety of gram-negative organisms, and obtained good results in 4. Olsen[9] mentioned briefly the successful use of the antibiotic by nebulization in 9 patients with bronchiectasis who had not responded to penicillin therapy and whose sputums contained a variety of gram-negative organisms. He pointed out that, whereas streptomycin treatment often eliminated gram-negative organisms from the sputum and thereby reduced both the cough and the volume of sputum, the primary bronchial dilatation was not affected, and the patients were still subject to the hazards of a deformed bronchial tree. Durant and his associates[10] reported 3 cases of pulmonary infections caused by *Haemophilus influenzae* that were treated by bronchoscopic instillation of streptomycin, supplemented in one case by parenteral administration. The results were uniformly good. The successful use of streptomycin in the treatment of single cases of pneumonia due to Friedländer bacillus has been reported by Learner and Minnich[11] and by Bishop and Rasmussen.[12] The series reported by the Committee on Chemotherapeutics and Other Agents of the National Research Council[13] includes 44 cases of acute or chronic pulmonary infections caused by various susceptible gram-negative bacteria in which 15 patients recovered, 18 improved and 11 showed no effect from streptomycin therapy. The clinical and bacteriologic observations in 6 cases of pulmonary infections treated with streptomycin are the subject of the present report.

MATERIALS AND METHODS

Patients were chosen for treatment with streptomycin from among regular admissions to the adult medical wards of the Boston City Hospital. They all had acute or chronic bronchopulmonary infections, or both, with various gram-negative bacilli as the only or predominating organisms in the sputums. In each case the organisms obtained before streptomycin treatment were sensitive to concentrations of this antibiotic that could usually be maintained in the plasma. Three patients had acute pneumonia, and the other 3 had chronic bronchopulmonary infections with acute exacerbations. One of the

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Most of the streptomycin used in this study was furnished by the National Research Council from supplies assigned for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents. This study was aided, in part, by a grant from the United States Public Health Service.

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latter also had a chronic suppurative otitis media. Except in one of the acute cases, penicillin with or without sulfonamides had been given before the beginning of streptomycin therapy and had produced no effect or only temporary improvement.

Sputum cultures were made in fluid mediums and on the surface of blood-agar plates. In Case 3 each specimen was also examined for pneumococci by the Neufeld method and was injected into mice, and the strains of pneumococci and Friedländer's bacilli were isolated and identified from cultures of peritoneal exudate and heart's blood of the mouse. The streptomycin sensitivity of pure cultures of the strains isolated and the levels of streptomycin in the plasma were determined by serial dilution methods in broth as described elsewhere.[14]

The streptomycin was given for the pulmonary infections by intramuscular and intravenous injections and by inhalation. The intravenous injections consisted of 1 gm. each dissolved in 20 cc. of physiologic saline solution and given at a rate not in excess of 1 cc. per minute to avoid or minimize the occurrence of histamine-like reactions. For intramuscular injections the streptomycin was dissolved in saline solution in amounts of 5 cc. for each gram, and the individual doses consisted of 0.5 or 1.0 gm. of the drug. The streptomycin inhalations were given in the manner recommended by Barach and his coworkers[15] for penicillin, 0.1 to 0.3 gm. in 1.0 or 1.5 cc. of saline solution being used each time. Instillations of streptomycin into the auditory canal were also employed for the treatment of the chronic otitic infection in Case 4. For that purpose a saline solution containing 25 mg. (25,000 units) per cubic centimeter was used. The doses in the individual cases are presented below in detail.

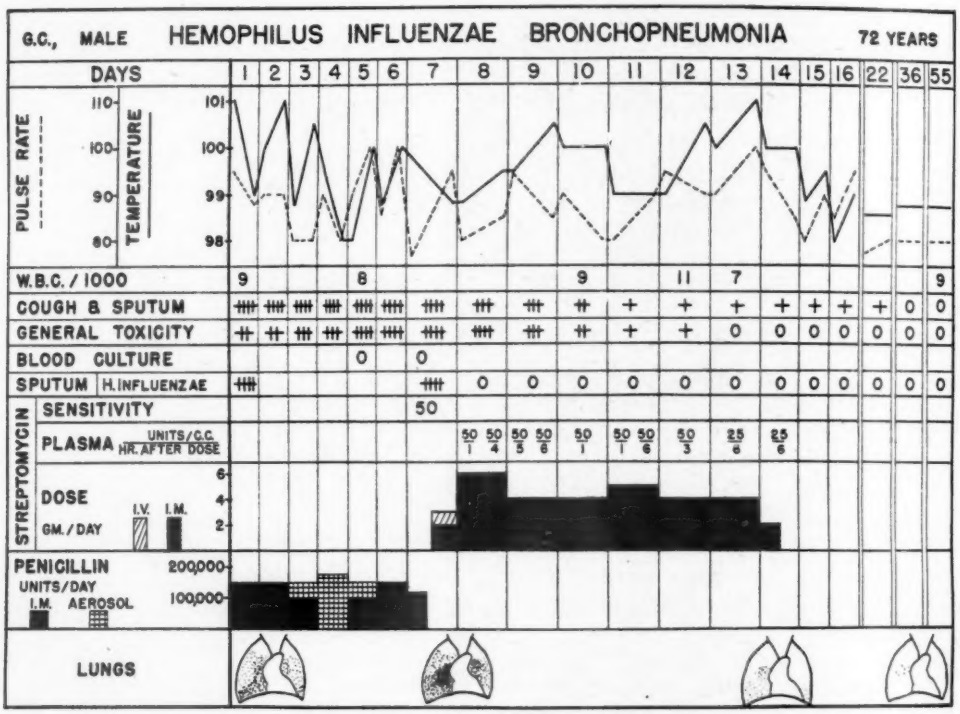

FIGURE 1. *Relevant Findings in Case 1.*

The acute pneumonic process in this case was superimposed on a chronic bronchitis and progressed during penicillin administration. Streptomycin therapy resulted in rapid clearing of H. influenzae *from the sputum, and clinical improvement followed. Cough and expectoration diminished steadily and then stopped completely. Fever persisted until after the streptomycin had been discontinued.*

CASE REPORTS

CASE 1. A 72-year-old retired cook entered the hospital on May 26, 1946. He had had a mild cough productive of small amounts of mucoid sputum for 15 years. Two weeks before entry the cough increased markedly, became productive of large amounts of purulent sputum and was accompanied by aching upper abdominal pain. The patient became increasingly dyspneic and developed marked abdominal distention. He denied having had fever, chills, pleuritic pain or bloody sputum. There had been a poor dietary intake for many years.

The patient appeared poorly nourished, dehydrated and acutely ill. The respirations were rapid and somewhat labored, and he coughed frequently and raised large amounts of yellow, purulent sputum. The lips and nail beds were moderately cyanotic. Both sides of the chest expanded equally and were resonant, but the breath sounds were diminished

over the right lower lobe and there were many medium crepitant rales over both lower lobes. A systolic murmur was heard along the right sternal border. The blood pressure was 135/82. The abdomen was distended and tympanitic, and there was some tenderness to deep palpation in the left upper quadrant.

Examination of the blood revealed a hemoglobin of 83 per cent (Sahli) and a white-cell count of 8600, with 53 per cent neutrophils, 40 per cent lymphocytes and 7 per cent monocytes. The blood Hinton reaction was negative. The nonprotein nitrogen of the blood was 71 mg. per 100 cc. A blood culture was negative, as was urinalysis. A sputum culture showed *H. influenzae* predominating and a few colonies each of *Streptococcus viridans*, *Escherichia coli* and diphtheroids. Roentgenograms of the chest showed thickening of both hilar roots, with infiltration of the surrounding regions. There were multiple nodular areas of density throughout the right middle and both lower lobes and a larger irregular area of density in the right lower lobe. The heart was moderately enlarged, and there was an aneurysmal dilatation of the ascending aorta.

The dehydration was promptly corrected by administration of fluids parenterally, and the blood nonprotein nitrogen dropped steadily to 35 mg. per 100 cc. Oxygen was given by nasal catheter with only slight improvement in the cyanosis and dyspnea, and the distention yielded only partially to repeated doses of prostigmine. Penicillin was given intramuscularly at first and then by inhalation. On the 5th day the patient became delirious and unco-operative, and it was necessary to discontinue the aerosolization and to readminister the penicillin by the intramuscular route.

On the 7th hospital day the patient was still acutely ill, dyspneic, febrile and completely disoriented. At that time there were signs of consolidation in the right lower lobe and numerous rales at both lung bases. The cough was still severe and productive of large amounts of purulent sputum, cultures of which yielded a pure and abundant growth of *H. influenzae*. These organisms were also seen in large numbers in direct smears of the sputum. The organism was inhibited in vitro by 50 units of streptomycin per cubic centimeter. Another blood culture showed no growth.

The penicillin was then stopped, and streptomycin was started. The initial dose was 1 gm. intravenously followed immediately by 1 gm. intramuscularly every 6 hours for a total of 32 gm. Within 36 hours after the first dose of streptomycin the patient showed decided improvement and became rational and well oriented, and the cough and sputum diminished markedly. On the 14th hospital day, when the streptomycin was stopped, the patient's appetite had returned, and his strength had improved so that he was able to sit up in a chair for several hours each day. The signs in the lungs had also cleared progressively, and only a few crepitant rales were heard, mostly over the right lower lobe. There was irregular fever at first, with a steady rise in temperature during the last 2 days of streptomycin therapy and a return to normal after the drug had been stopped. Direct smears and cultures of the sputum 24 hours after the first dose of streptomycin and repeatedly thereafter failed to show any influenza bacilli. Convalescence was uneventful except for repeated episodes of urinary retention. By the end of the 5th week the cough had completely stopped and the lungs were clear on both physical and x-ray examination.

The course, therapy and some relevant findings in this case are presented in Figure 1.

Case 2. A 54-year-old shoemaker entered the hospital on July 3, 1946. He had had an attack of pneumonia 10 years previously and a chronic productive cough since that time. During the year before admission he noted weakness and increasing fatigue. On the day before entry he developed fever and right-sided pleuritic pain. The cough increased, and he began to raise blood-tinged sputum.

The patient appeared acutely ill and dehydrated and was coughing frequently and raising tenacious rusty sputum. Dullness, bronchial breathing and crepitant rales in the right axilla were the only positive physical findings. The temperature was 102°F., the pulse 100, and the respirations 25.

Examination of the blood disclosed a hemoglobin of 75 per cent (Sahli) and a white-cell count of 11,500, with 86 per cent neutrophils. The blood nonprotein nitrogen was 126 mg. per 100 cc. A blood Hinton test was positive. Urinalysis was negative. Microscopical examination of the stained sputum showed numerous large encapsulated gram-negative bacilli, and a culture revealed a Type A Friedländer bacillus. A blood culture showed no growth. A roentgenogram of the chest revealed dense consolidation of the peripheral portion of the right middle lobe and of the lower portion of the right upper lobe.

The antibacterial therapy and the course of the disease are shown in Figure 2. The patient was given parenteral fluids and oxygen by nasal catheter. Codeine and Demerol were used to relieve pleuritic pain. Forty thousand units of penicillin was given intramuscularly every 3 hours. On the 3rd hospital day, after adequate hydration had been obtained and the blood nonprotein nitrogen had fallen to 46 mg. per 100 cc., the patient was given sulfadiazine in full doses by mouth. In spite of this therapy he showed no clinical improvement. The white-cell count increased, Friedländer bacilli persisted in large numbers in the sputum and an x-ray film of the chest showed extension of the consolidation to the remainder of the right middle and most of the right upper lobes. The penicillin and sulfadiazine were both discontinued on the 6th day, and streptomycin therapy was then begun. The initial dose was 1 gm. intravenously and a similar amount intramuscularly, and this was followed by 1 gm. every 6 hours.

Within 48 hours, the patient appeared less dyspneic, and the temperature and pulse rate dropped somewhat. A sputum culture obtained 6 hours after the initial dose of streptomycin showed only 15 colonies of Friedländer's bacillus and this organism was not found in the culture made after the 2nd day of streptomycin therapy. The gross appearance of the sputum, however, showed no change during this interval. A roentgenogram of the chest on the 4th day of streptomycin treatment showed no extension of the pulmonary process, but small areas of increased radiance were seen within the right middle lobe. In spite of the clinical and bacteriologic improvement, the patient expired suddenly on the 4th day of streptomycin therapy after a total of 15 gm. of streptomycin had been given.

Autopsy. Post-mortem examination revealed dense, grayish consolidation of the right upper and middle lobes and numerous small, thin-walled abscesses throughout the consolidated areas. The contents of the abscesses and the alveolar and bronchial exudate were thick, mucoid and stringy and yielded Type A Friedländer bacilli on culture. No evidence of embolism was found. The organism obtained at autopsy was inhibited in vitro by 0.8 units of streptomycin per cubic centimeter — a value identical with the minimum inhibiting concentration before treatment.

Case 3. A 54-year-old bartender was admitted to the hospital on September 12, 1946. A week previously he had developed a cold with coryza, and 2 days later he began to have severe pleuritic pain in the right anterior chest and a cough productive of purulent sputum. He had had pneumonia 14 years previously and two brief episodes of pleuritic pain during the preceding 4 years, but there had been no chronic cough or cardiac symptoms.

On admission the patient appeared acutely ill and in a shock-like state; the skin was flushed and moist, the tongue was dry, and the lips and fingernails slightly cyanotic. There were signs of consolidation of the lower half of the right side of the chest anteriorly, and a few medium crepitant rales were heard throughout the left posterior portion. The heart was not enlarged and no murmurs were heard, but the rhythm was totally irregular. The temperature was 98.6°F., the pulse 120 and thready, and the respirations 32 and labored. The blood pressure was 95/55.

Examination of the blood disclosed a hemoglobin of 110 per cent (Sahli), a hematocrit of 43 per cent and a white-cell count of 25,000, with 96 per cent neutrophils, half of which were young forms. The blood nonprotein nitrogen was 42 mg. per 100 cc. The blood Hinton reaction was negative. The urine contained a trace of albumin, and there were many fine granular casts in the sediment. An arm-to-carotid-sinus circulation time was normal, and the electrocardiogram showed only auricular fibrillation.

A blood culture was positive for a Type C Friedländer bacillus.* The sputum was tenacious, purulent and bloody, and a stained smear showed it to contain innumerable large, encapsulated gram-negative bacilli and a few gram-positive lanceolated diplococci. A Neufeld test with anti-pneumococcus serums showed a reaction of some of the diplococci with Type 19 antiserum. Cultures of the sputum on blood-agar plates yielded only Friedländer bacilli, but this organism and a Type 7 pneumococcus were obtained from after treatment were negative. Friedländer bacilli persisted in the sputum in varying numbers. Pneumococci were looked for in the sputum by all available methods. Type 7 pneumococci were isolated on only one more occasion, but Type 19 pneumococci, which had been seen in the fresh Neufeld preparation of the sputum on admission, were not observed again until they were isolated on the 8th day.

On the 5th day, signs of cavitation of the right middle lobe were made out and confirmed by x-ray study. Because of

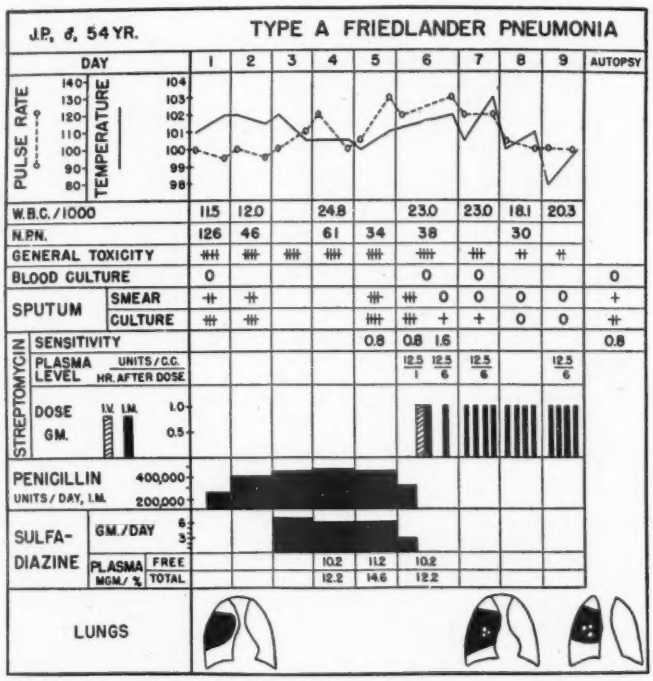

FIGURE 2. *Relevant Findings in Case 2.*

The pneumonia progressed and organisms persisted in the sputum in large numbers during treatment with penicillin and sulfadiazine. Streptomycin therapy was followed by definite clinical improvement and elimination of Friedlander bacilli from smears and cultures of the sputum. The consolidation and abscess formation that are typical of Friedlander pneumonia were found at autopsy in the right upper and middle lobes, and moderate numbers of organisms were obtained in cultures from these lobes. No other cause of the sudden death was found.

cultures of the heart's blood of a mouse inoculated with the sputum.

The patient was given fluids parenterally and by mouth, as well as small doses of morphine and codeine to relieve the pleuritic pain, and digitalization was begun. Because of the characteristic findings in the sputum, a diagnosis of pneumonia due to a Friedländer bacillus was made, and intramuscular streptomycin was begun promptly with 1 gm. every 4 hours for 2 days and then every 6 hours for 4 more days. The usual initial intravenous injection was not given in this case because of the danger that a histamine-like reaction would aggravate the shock-like state of the patient.

The therapy, course and bacteriologic findings are presented in Figure 3. The patient's general condition began to improve within a few hours. He then became progressively stronger and more active; the appetite returned, the pleuritic pain diminished, the breathing became easier and the blood pressure rose to 120/80. Auricular fibrillation continued until the 9th day, when normal sinus rhythm was restored. Blood cultures taken on four occasions during the first 2 days

*The cultures of Friedländer's bacilli in this case were all typed at the Bureau of Laboratories of the New York City Department of Health through the courtesy of Miss Annabel Walter.

this finding and because of increasing pain and tenderness at the injection sites, the intramuscular administration of streptomycin was discontinued, and subsequent doses were given by the inhalation of 125 mg. dissolved in 1 cc. of saline solution ten times daily. Each inhalation was preceded by a 5-minute period of postural drainage. On this regime the patient continued to improve, and the number of Friedländer bacilli in the sputum decreased. On the 10th day, because of the persistence of large numbers of Type 19 pneumococci in the sputum associated with a rising temperature, the patient was also given 100,000 units of penicillin intramuscularly every 8 hours. The temperature dropped promptly, and the number of pneumococci in the sputum diminished markedly. Both the penicillin and streptomycin were discontinued on the 17th day. At that time the patient had only a slight residual cough, raised moderate amounts of purulent sputum and had some sweating at night. Roentgenograms still showed the area of consolidation with several small abscesses.

During the next 2 months the patient remained afebrile and symptom free, and regained much weight and strength. The area of pulmonary consolidation diminished in size and showed some evidence of fibrosis. The abscesses became

gradually smaller and finally could no longer be made out. Friedländer bacilli continued to be the predominant organisms in the sputum cultures, but the Type 19 pneumococci could not be isolated after the 3rd week.

The streptomycin and penicillin sensitivities of the various organisms isolated at different times during and after therapy are shown in Figure 3. The Friedländer bacilli (all the strains were Type C) increased in resistance to streptomycin abruptly and markedly on the 3rd day and remained resistant thereafter. The streptomycin sensitivity of the Type 7 pneumococcus was the same before therapy and on the 5th day. purulent discharge from the left ear, and small perforations were seen in both tympanic membranes. Numerous crepitant rales were heard over the right middle lobe and both lower lobes of the lungs, but no signs of consolidation were made out. The sputum was profuse and mucopurulent.

Urinalysis and the hematologic findings were negative. Repeated blood Wassermann and Hinton tests were positive, but those of the spinal fluid were negative. Roentgenograms of the chest showed mottled densities of the right middle-lung field and peribronchial thickenings in both lower lobes. Films of the mastoid processes revealed thickening of the

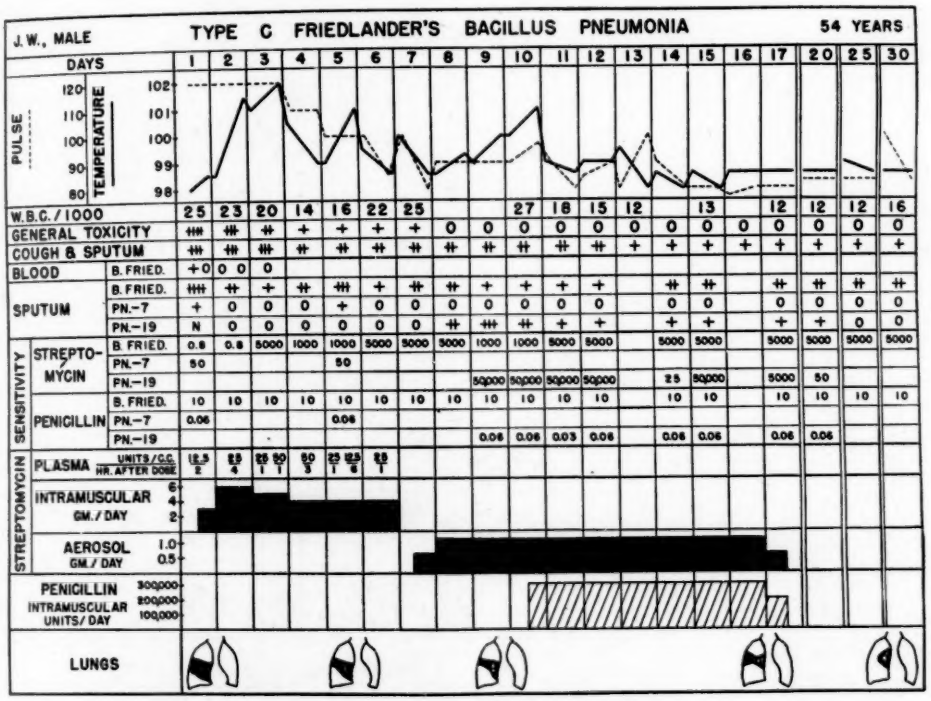

FIGURE 3. *Relevant Findings in Case 3.*

The Friedlander bacillus bacteremia cleared promptly and the patient improved steadily after streptomycin was started. The bacilli persisted in the sputum and became resistant to streptomycin. Both streptomycin-resistant and streptomycin-sensitive strains of Type 19 pneumococci were obtained, but there was no change in the penicillin-sensitivity of any of the strains.

The Type 19 pneumococcus, although seen earlier in the direct Neufeld typing, was not obtained from the cultures at that time and could not, therefore, be tested for streptomycin sensitivity. When isolated for the first time it was found to be totally resistant to streptomycin, but much more sensitive strains of this type were isolated on two occasions during and after the streptomycin aerosolization. The penicillin sensitivity of all the strains of these three organisms remained unchanged throughout.

CASE 4. An 18-year-old single clerk had had a productive cough and suppurative otitis media since the age of 4 and an attack of lobar pneumonia at the age of 14. In January, 1946, she was admitted to the hospital with pneumonia due to a Type 4 pneumococcus of both lower lobes and was treated with penicillin and sulfadiazine. At that time she was found to have serologic evidence of syphilis. She made a seemingly uneventful recovery from the pneumonia and was discharged after 17 days, although cough and expectoration continued and numerous crepitant rales were still heard at both lung bases.

In April, the patient was readmitted primarily for further penicillin therapy because of the persistence of positive serologic tests for syphilis. Physical examination revealed no evidence of that disease. There was a moderate amount of petrous bones, with bilateral obliteration of the mastoid cells. Stained smears of the sputum and of the aural exudate disclosed numerous large, encapsulated gram-negative bacilli, and cultures of both showed abundant colonies of Type A Friedländer bacilli.

The patient was given a course of penicillin consisting of 20,000 units intramuscularly every 3 hours for 8 days. At the end of that time there were no changes in the pulmonary or aural findings, and Friedländer bacilli were found repeatedly in cultures of the ear and of the sputum. Cultures of these organisms obtained at different times were completely inhibited by 0.8 or 1.6 units of streptomycin per cubic centimeter. Small numbers of *Staphylococcus albus*, inhibited by 12.5 units of streptomycin, were also obtained from cultures of the aural discharge.

Streptomycin therapy was begun on the 12th day in an attempt to influence the infection in the lungs and in the left ear. The relevant data are shown in Figure 4. The dose of streptomycin was 0.5 gm. in 2.5 cc. of physiologic saline solution intramuscularly every 6 hours and 25 mg. (25,000 units) in 1 cc. of saline solution instilled into the left auditory canal every 8 hours. The intramuscular injections were discontinued on the 4th day because of severe gluteal tenderness, and inhalations of 0.3 gm. in 1.5 cc. of saline were given instead, seven times a day for 9 days.

There was a gradual decrease in the amount of cough and sputum after the streptomycin had been started, and the discharge from the left ear stopped completely after the 3rd day. Sputum cultures continued to yield Friedländer bacilli for 4 days, but the numbers of characteristic colonies of this organism on surface plates declined rapidly during that time and then could not be found in the sputum cultures made after the 1st day of aerosol therapy. The strain isolated on the 4th day was inhibited by 25 units of streptomycin per cubic centimeter, representing a thirty-two-fold increase in resistance over that found before treatment was begun. Colonies of *H. influenzae* were isolated from the sputum for the first time on the 4th day of streptomycin therapy and anterior chest for which a physician prescribed codeine. On the day before entry she had chills, fever, increased cough and blood-stained sputum.

On admission the patient was acutely ill and in marked respiratory distress. The respiratory excursions of the left chest were restricted, and there were dullness, diminished tactile fremitus, voice and breath sounds and medium moist rales throughout the left lower lobe. The abdomen showed the uterine enlargement of the third trimester of pregnancy.

The temperature was 102.4°F., the pulse 140, and the respirations 30.

Examination of the blood disclosed a red-cell count of 3,830,000, with a hemoglobin of 63 per cent (Sahli), and a

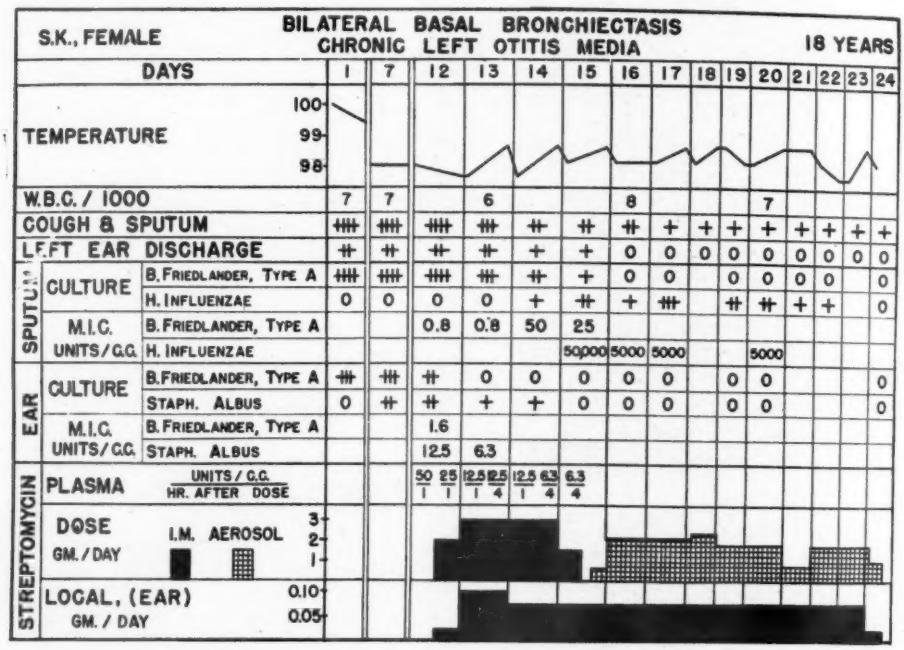

FIGURE 4. *Relevant Findings in Case 4.*

repeatedly thereafter until the last day of that treatment. The organisms required between 5000 and 50,000 units of streptomycin per cubic centimeter for complete inhibition of growth. Cultures of the exudate from the left ear were negative for Friedländer bacilli after the 1st day of streptomycin therapy and for *Staph. albus* after the 3rd day.

The patient was discharged from the hospital after 12 days of streptomycin treatment. At that time the left ear had remained dry; the cough and sputum were markedly decreased, but the auscultatory and roentgenographic signs in the chest were essentially unchanged. Two weeks later she was readmitted to the hospital with lobar pneumonia involving the left lower lobe. A Type 2 pneumococcus was obtained in pure culture from typical rusty sputum. The patient recovered promptly following penicillin therapy. Numerous cultures were negative for both Friedländer bacilli and *H. influenzae* before and during this therapy and during a follow-up period of 2 months. Crepitant rales persisted throughout both lower lobes during this period, and roentgenograms continued to show peribronchial thickening.

CASE 5. A 25-year-old married woman, in the 7th month of pregnancy, was admitted to the hospital on May 27, 1946. She had had five attacks of pneumonia, a chronic productive cough since the age of 6 and an attack of "pleurisy" in 1945. At the age of 15, she had suddenly had a gross hemoptysis and was studied at another hospital, where a diagnosis of bronchiectasis was made. One week before admission she developed severe and persistent pleuritic pain in the left white-cell count of 42,700, with 93 per cent neutrophils. A blood culture was negative. The nonprotein nitrogen was normal. A blood Hinton test and urinalysis were negative. The sputum was mucopurulent and contained no blood and on culture yielded *S. viridans, H. influenzae, Esch. coli* and occasional colonies of Type A Friedländer bacilli. An x-ray film of the chest showed evidence of some fluid on the left and consolidation in the left lower lobe.

The patient was given oxygen by nasal catheter, morphine initially and then codeine for control of the pleuritic pain and 30,000 units of penicillin intramuscularly every 2 hours. A left thoracentesis, performed on the 2nd day, yielded 150 cc. of greenish-yellow, cloudy, malodorous fluid that contained 26,000 pus cells per cubic millimeter. Cultures of the fluid yielded a slowly growing unidentified, gram-negative bacillus. After this thoracentesis 200,000 units of penicillin was injected into the pleural cavity. Another thoracentesis on the 4th day yielded 20 cc. of purulent fluid that had no odor and gave no growth. One hundred thousand units of penicillin was injected intrapleurally at that time. Further attempts failed to obtain fluid.

On this regime the patient improved considerably. The temperature, pulse and respiratory rates dropped gradually, and the white-cell count fell to 20,000 but severe cough and profuse expectoration continued. On the 6th day penicillin was given by inhalation as well as intramuscularly; the dose was 25,000 units dissolved in 1 cc. of isotonic sodium chloride solution aerosolized every 3 hours. During 1 week of this therapy, the patient continued to improve clinically, and

x-ray films of the chest revealed some resolution of the pneumonic process, but the severe cough continued and was still productive of large amounts of greenish, purulent sputum. Repeated cultures of the sputum revealed only *H. influenzae* (inhibited by 1.6 units of streptomycin per cubic centimeter) and *Aerobacter aerogenes* (inhibited by 6.3 units of streptomycin).

On the 14th day the penicillin by inhalation was discontinued, and streptomycin was given by this route in an attempt to diminish the cough and sputum. The dose was 300,000 units in 1 cc. of isotonic sodium chloride solution aerosolized five times daily. The administration of 30,000 units of penicillin intramuscularly every 2 hours was continued during the streptomycin inhalation treatment. There was a marked reduction in the cough and sputum within 48 hours after streptomycin was begun, and during the last 3 of the 5 days of this therapy it was difficult to obtain sputum for bacteriologic examination. No trace of *H. influenzae* could be found in any of the sputum cultures after the 1st day of streptomycin treatment; *A. aerogenes* likewise disappeared from the sputum for 48 hours but reappeared in small numbers on the 3rd day of treatment. The strain isolated on that day had cultural and biochemical properties identical with those of the pretreatment strains, but it grew uninhibited in 50,000 units of streptomycin per cubic centimeter. Two subsequent specimens of sputum that the patient was able to produce after therapy also contained small numbers of *A. aerogenes* that were totally resistant to streptomycin.

The streptomycin inhalations were discontinued after 5 days, and penicillin aerosolization reinstituted. During the 4th week of hospitalization, the patient had no symptoms; the temperature, pulse and respiration were normal, and the white-cell count was 12,000. X-ray films of the chest, however, showed persistence of density in the left lower lobe with marked pleural thickening. On the 29th day the patient left the hospital against advice, and subsequent follow-up studies were not possible.

Comment. In this case the relief from the acute pulmonary infection and the probable cure of the putrid empyema must be ascribed largely to the use of penicillin, which was given intramuscularly and by inhalation and, on two occasions, intrapleurally. The pleural exudate, although it yielded a gram-negative bacillus, was apparently sterilized on this regime. Streptomycin inhalations were probably responsible for a marked reduction in the cough and expectoration and the rapid elimination of *H. influenzae* from the sputum. *Aerobacter aerogenes*, however, persisted and rapidly became resistant during the streptomycin therapy. The pregnancy was unaffected.

Case 6. A 44-year-old clerk entered the hospital on December 8, 1945. He had been in excellent health until about 2 years before admission, when he developed a cough that persisted and was productive of yellowish and occasionally blood-streaked sputum. He also began to have moderate dyspnea on exertion. Two weeks before entry, he noted an increase in the cough, a reappearance of blood-streaked sputum and some chilliness, fever, malaise and anorexia. High fever, shaking chills and right anterior pleuritic pain began 5 days before admission.

The patient appeared well developed, poorly nourished, dyspneic and acutely ill. The lips and nail beds were cyanotic, and there was moderate clubbing of the fingers. The voice was hoarse, owing to paresis of the left vocal cord. There were typical signs of consolidation of the right lower lobe, and medium crepitant rales and rhonchi were heard over the left lower lobe. The temperature was 102.5°F., the pulse 120, and the respirations 32.

Examination of the blood showed a hemoglobin of 98 per cent (Sahli) and a white-cell count of 16,600, with 84 per cent neutrophils. Blood cultures and urinalysis were negative. Sputum cultures revealed *Staph. albus*, *Micrococcus catarrhalis*, *Str. viridans* and *H. influenzae*. Roentgenograms of the chest showed consolidation of the right lower and middle lobes and patchy areas of density in the left lower lobe.

The antibacterial therapy, the relevant bacteriologic findings and some aspects of the course of the disease over a 5-month period are presented in Figure 5. On admission oxygen was administered by nasal catheter, and 20,000 units of penicillin was given intramuscularly every 2 hours. After 7 days the penicillin was discontinued. At that time there was definite clinical improvement, as well as a decrease in the white-cell count and physical signs of resolution in the right lower and middle lobes, but the cough continued to be productive of large amounts of purulent sputum.

Three days after the end of penicillin therapy the patient had a shaking chill; the temperature rose to 103°F., and all the symptoms recurred. The white-cell count rose to 15,000. A blood culture was negative, however, and no extension of the pulmonary consolidation could be demonstrated. Sulfadiazine was then given by mouth in a dose of 4 gm. followed by 1 gm. every 4 hours for 3 days, when a generalized scarlatiniform rash appeared. Sulfathiazole in the same dosage was then substituted for the sulfadiazine, and penicillin was again given in doses of 20,000 units intramuscularly every 3 hours. The rash was later proved to have been due to barbiturates rather than to sulfadiazine. There was a gradual subsidence of the fever and the acute symptoms, and sulfathiazole was omitted after 10 days.

For the next 5 weeks there were no acute symptoms, and the temperature remained normal. The patient, however, lost weight steadily, developed severe night sweats, and continued to have severe cough and to produce abundant purulent sputum, averaging 150 to 200 cc. a day. During that time dietary and vitamin supplements were administered, and postural drainage was carried out every 2 hours. Bronchoscopic examination revealed profuse purulent secretions from both lower lobes but no evidence of a tumor, stenosis or a foreign body.

During the following 6 weeks the patient was given penicillin by inhalation in doses of 25,000 units at first and later 50,000 units dissolved in 1 cubic centimeter of physiologic saline solution every 3 hours, each dose being preceded by postural drainage. He showed considerable clinical improvement on this regime; his strength and weight increased, and he was able to sit up in a chair and to walk short distances. There was no reduction, however, in the quantity of sputum raised, and x-ray films of the chest revealed marked peribronchial thickening in the right lower lobe and small spotty areas of infiltration throughout the right lower and middle and left lower lobes. These findings were interpreted as indicating advanced bronchiectasis.

During the 15th week the patient suffered a serious relapse. He was seated in a chair when he suddenly became extremely dyspneic and cyanotic and rapidly developed profound shock. Loud "gurgling" sounds were audible throughout the chest, suggesting the presence of acute pulmonary edema, but there was no venous distention and an electrocardiogram showed no abnormality except tachycardia. The presence of a ruptured lung abscess appeared likely. The patient was put in a position for postural drainage, and 200 cc. of yellowish-green, malodorous pus immediately drained from the trachea. The foot of the bed was elevated, and he was given oxygen by mask and intramuscular injections of caffeine. Postural drainage was carried out frequently and he was again given 30,000 units of penicillin intramuscularly every 2 hours and sulfadiazine in full doses by mouth. An x-ray film of the chest taken with a portable apparatus showed diffuse haziness and patchy infiltration throughout both lung fields. Cultures of the purulent sputum at that time revealed colonies of *Staph. aureus* and *H. influenzae*, and blood cultures were negative.

The patient remained in a precarious condition for 5 days, but the temperature, pulse and respirations began to drop and the cyanosis lessened. Marked weakness, sweating, anorexia and cough with large amounts of sputum continued. Stained smears of the sputum revealed large numbers of small, pleomorphic, gram-negative coccobacilli, and repeated cultures showed many colonies of *H. influenzae* (sensitive to 1.6 units of streptomycin per cubic centimeter) with small numbers of *Staph. aureus* colonies (inhibited by 25 units of streptomycin and 7.5 units of penicillin).

Seventeen weeks after admission, treatment with streptomycin by inhalation was started with a dose of 250,000 units dissolved in 1.5 cc. of physiologic saline solution every 2 hours during the day and every 4 hours at night. Each inhalation was carried out immediately after postural drainage, and this therapy was continued for 13 days.

There was no clinical improvement after 5 days of this therapy, however, and large numbers of *H. influenzae* persisted in smears and cultures of the sputum. After 6 days, 1 gm. of streptomycin was given intravenously in 20 cc. of physiologic saline solution four or five times daily in addition

to the aerosolized streptomycin. It was necessary to administer the intravenous injections at the rate of 1 cc. or less a minute, for the patient developed flushing, faintness, headache and vertigo when the drug was given at a faster rate. A total of 33 gm. was given intravenously over an 8-day period.

The patient showed no clinical improvement during the 13 days of streptomycin therapy, and he continued to cough up 250 to 500 cc. of thick purulent sputum daily. Cultures of the sputum showed a rapid disappearance of the staphylococcus, but *H. influenzae* persisted in almost pure culture. The strain of *H. influenzae* isolated 24 hours after the initial aerosolized dose grew well in the presence of 5000 units of streptomycin per cubic centimeter, and the sensitivity of the remaining strains isolated during treatment ranged from 500 to over 5000 units.

Because of the lack of clinical response and the development of fastness by the organism the streptomycin was stopped. Three days later the patient became acutely ill, with fever, increased pulse and respiratory rates and signs of right lower-lobe consolidation. Sputum cultures yielded colonies of *Staph. aureus* that were not inhibited by 50,000 units of streptomycin and of *H. influenzae* that were inhibited by 500 units. Supportive measures and sulfadiazine were given, but the patient became progressively worse and died at the end of the 20th week.

Autopsy. Post-mortem examination revealed reddish-gray consolidation of all lobes except the left upper one. There was extensive dilatation of all bronchi, whose walls were thin but surrounded by fibrotic tissue. Just above the tracheal bifurcation, there was a fleshy, yellowish mass of tumor tissue that had grown through the tracheal wall and extended down the lateral wall of the right main-stem bronchus. The mediastinal lymph nodes were enlarged, firm and filled with carcinomatous tissue. Cultures from the lungs yielded small numbers of *Staph. aureus*, inhibited by 100 units of streptomycin per cubic centimeter, and a heavy growth of *H. influenzae*, inhibited by 5000 units of streptomycin. The final pathological diagnoses were epidermoid carcinoma of the trachea and right main-stem bronchus, with local extension into the mediastinum, chronic pneumonitis of the entire right lung and of the left lower lobe and diffuse bilateral bronchiectasis.

Results

The clinical and bacteriologic results are briefly summarized in Table 1. The first 3 patients received streptomycin for severe pneumonia, which in 2 cases had not responded to treatment with penicillin, supplemented in Case 2 with sulfadiazine.

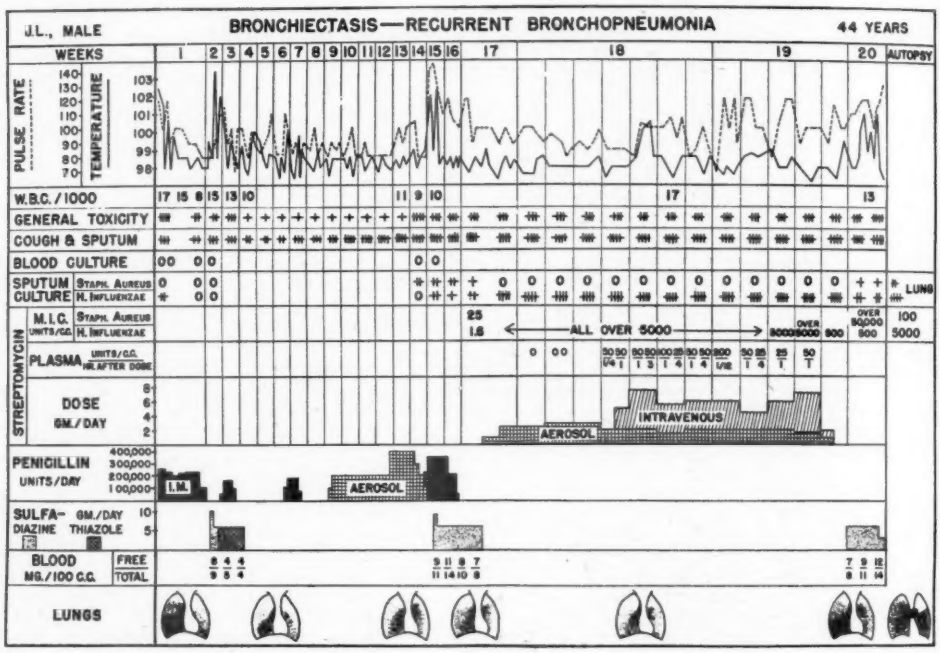

FIGURE 5. *Relevant Findings in Case 6.*

The bronchopulmonary infection was temporarily and only partially improved by sulfonamides and penicillin. Streptomycin therapy was without effect and resulted in the appearance of resistant bacteria in the sputum. Autopsy revealed a bronchogenic carcinoma in addition to extensive pneumonitis and bronchiectasis.

Case 2 ended fatally, but in all 3 cases there was bacteriologic evidence of improvement after streptomycin had been started.

Case 1 was in an aged patient with an extensive pneumonia due to *H. influenzae*. The prognosis at the beginning of streptomycin therapy was considered poor. Rapid clinical improvement followed soon after treatment with streptomycin had been started. The cough and sputum diminished promptly, and the pneumonic process cleared rapidly and then completely. The strain of *H. influenzae* that had been of relatively low susceptibility before treatment rapidly disappeared from the sputum cultures and did not reappear during the follow-up studies.

Case 2 was a pneumonia due to a Type A Friedländer bacillus in which there was no clinical or laboratory evidence of improvement after five days

of intramuscular penicillin, supplemented during the last three and a half days with oral sulfadiazine. The blood culture was negative before and at the end of this therapy. Streptomycin alone was given intramuscularly, and there was definite clinical and bacteriologic improvement. The patient died suddenly on the fourth day of treatment, and autopsy disclosed anatomic findings characteristic of pneumonia due to Friedländer bacillus, with abscess purulent sputum. The Friedländer bacillus isolated from the sputum on the third day of streptomycin treatment was highly resistant to the action of this drug, and a similar resistance was demonstrated by all the remaining strains of this organism isolated during and after the streptomycin therapy. Shortly after streptomycin had been given by aerosolization, large numbers of Type 19 pneumococci, also highly resistant to streptomycin, were isolated from the

TABLE 1. *Organisms Isolated from the Sputum in Relation to Minimum (Complete) Inhibiting Concentration of Streptomycin.*

Case No.	Streptomycin Therapy		Organism before Therapy	Inhibiting Concentration of Drug	Organism during Therapy	Inhibiting Concentration of Drug	Organism after Therapy	Inhibiting Concentration of Drug	Development of Resistance to Streptomycin		Clinical Result
	Route	Amount							Interval	Amount	
		gm.		*units/cc.*		*units/cc.*		*units/cc.*	*days*	*gm.*	
1	Intravenous Intramuscular	1.0 32.0	*H. influenzae*	50.0	—	—	—	—	—	—	Cure
2	Intravenous Intramuscular	1.0 14.0	Type A Friedländer bacillus	0.8	—	—	Type A Friedländer bacillus*	0.8	—	—	Death
3	Intramuscular	26.0	Type C Friedländer bacillus	0.8	Type C Friedländer bacillus	1,000–5,000	Type C Friedländer bacillus	5,000	2	10.0	Recovery, with abscess formation
	Inhalation	12.5	Type 7 pneumococcus	50.0	Type 7 pneumococcus	50	—	—	—	—	
			Type 19 pneumococcus	—	Type 19 pneumococcus	25.0–50,000	Type 19 pneumococcus	50	8	26.0	
4†	Intramuscular Inhalation	8.5 16.0	Type A Friedländer bacillus	0.8	Type A Friedländer bacillus *H. influenzae*	25–50 5,000–50,000	*S. viridans*	—	2	6.0	Decreased cough and sputum; lung signs unchanged.
5	Inhalation	7.5	*A. aerogenes* *H. influenzae*	6.3 1.6	*A. aerogenes*	>50,000	*A. aerogenes*	>50,000	3	4.5	Decreased cough and sputum; lung signs unchanged.
6	Inhalation	27.0	*H. influenzae*	1.6	*H. influenzae*	50,000	*H. influenzae*	500–50,000	1	2.0	Temporary improvement
	Intravenous	33.0	*Staph. aureus*	25.0			*Staph. aureus*	>50,000	13	60.0	Death; bronchogenic carcinoma found at autopsy.

*Revealed on culture from lung at autopsy.

†In this case 8 gm. of streptomycin was instilled into the left ear. The pretreatment culture of the aural discharge showed Type A Friedländer bacilli with a minimum inhibiting concentration of 1.6 units per cubic centimeter, and *Staph. albus*, with a minimum inhibiting concentration of 12.5 units per cubic centimeter. A strain of the *Staph. albus*, with a minimum inhibiting concentration of 6.25 units per cubic centimeter, was obtained on the second day of treatment.

formation, in most of the right upper and middle lobes. Although Friedländer bacilli could not be obtained from the sputum during the last two days of therapy, they were recovered from the lungs at autopsy and were then found to be as sensitive to streptomycin as the pretreatment strains.

Case 3 was one of severe pneumonia due to a type C Friedländer bacillus, with bacteremia. The patient was in a shock-like state and almost moribund at the time of admission. Antibacterial therapy during the early acute stage was limited to intramuscular streptomycin. This produced a prompt clearing of the bacteremia and marked clinical improvement. The pulmonary infection, however, instead of clearing completely, became chronic, and definite abscesses formed. Although the patient was afebrile and free of systemic symptoms for three months after treatment, he continued to cough and to produce large amounts of sputum. After seven days of treatment with intramuscular penicillin, the numbers of pneumococci diminished markedly, although a few colonies of these organisms and many colonies of Friedländer bacilli were repeatedly found in the sputum cultures made during and after the course of penicillin. It is of interest that, whereas both the gram-positive and the gram-negative organisms became markedly resistant to streptomycin during treatment with this antibiotic, neither strain showed any change in sensitivity to penicillin during or after administration of that agent.

The 3 remaining cases represent chronic and recurrent bronchopulmonary infections in which gram-negative bacilli were found in large numbers in the sputum. The streptomycin was used in these cases in an attempt to reduce the amount of cough and sputum by inhibiting or eliminating the gram-negative flora. Each of these patients had received

a fairly long course of penicillin intramuscularly, and 2 of them had also received that antibiotic by inhalation with only partial or temporary relief before streptomycin treatment was started.

In Cases 4 and 5 definite clinical improvement occurred after the streptomycin had been begun. The cough was markedly reduced, and the small amounts of sputum that the patients continued to raise appeared clear rather than purulent. In Case 4, except during the brief attack of Type 2 pneumococcus pneumonia of the left lower lobe that occurred two weeks after streptomycin treatment, the lung findings were essentially unchanged for three months. In this case a thirty-two-fold increase in streptomycin resistance was demonstrated by the Friedländer bacillus, and a strain of *H. influenzae* isolated during treatment was highly resistant to the action of that drug. Neither of these organisms, however, was recovered from sputum cultures during a three-month period after streptomycin treatment.

Of particular interest in Case 4 was the rapid clearing of the purulent discharge from the left ear following the intramuscular and topical streptomycin therapy. Many different types of local and systemic therapy, including long courses of penicillin and sulfonamides, had previously failed to accomplish this result. The ear remained dry and the cultures free of Friedländer bacilli throughout the follow-up period.

Adequate follow-up studies were not conducted in Case 5, but the lung findings were also essentially unchanged ten days after the conclusion of streptomycin therapy. Small numbers of a resistant strain of *A. aerogenes* were recovered from sputum cultures both during and after treatment.

In Case 6 there was no improvement in spite of large doses of streptomycin intravenously and by inhalation, and the patient died soon after this therapy was concluded. *H. influenzae*, the predominant organism in sputum cultures, persisted throughout the period of therapy. There was a marked increase in streptomycin-resistance of this organism within twenty-four hours of treatment. In this case the chronic pulmonary infection was associated with a bronchogenic carcinoma whose diagnosis had been suspected during life but was definitely established only at autopsy.

Untoward Reactions

These were infrequent and minimal. Pain and tenderness in the region of the intramuscular injections were noted in every case, and in Case 4 the sites became red and indurated. Increasing fever during the latter part of the course of streptomycin in Case 1 was probably due to streptomycin, since the temperature dropped steadily after the antibiotic was discontinued. In Case 6 the intravenous injections were accompanied by faintness, flushing and headache when the solution was given at too rapid a rate. There were no untoward reactions to the nebulized streptomycin in any of the patients. Disorders of labyrinthine or eighth-nerve function were not observed in these cases.

Streptomycin Levels

In all the patients who received streptomycin by the intravenous or intramuscular route, the levels of streptomycin in the plasma measured at various intervals following individual injections throughout therapy were, for the most part, equal to or higher than the in vitro sensitivity of the infecting organisms that had been obtained before treatment. The levels corresponded, in general, to those obtained in other patients receiving similar doses of streptomycin. Progressive increases in streptomycin levels in the blood were not observed. Blood obtained from 3 patients during and at short intervals after the aerosolization of streptomycin, when they were not receiving systemic therapy, failed to show detectable amounts of the antibiotic.

Discussion

It is not possible to draw final conclusions regarding the value of streptomycin in pulmonary infections, because relatively few cases have been treated. The clinical results, however, in this small series of cases and in those reported in the literature indicate that some patients with pneumonia and certain others with recurrent or chronic bronchopulmonary infections caused by gram-negative bacilli respond favorably to streptomycin therapy. In some cases this drug seems to be life-saving. There are other patients, however, who seem to derive little or no benefit from large doses of streptomycin and in whom the infection may become or remain chronic or may terminate fatally. In certain cases the poor results may be associated with the rapid development of streptomycin fastness by the infecting organisms.

The recovery of streptomycin-resistant bacterial strains during and after treatment in patients with urinary-tract infections,[14, 16–18] meningitis,[6, 7, 19] tuberculosis,[20] osteomyelitis[21] and ozena[9] has been reported, but the same phenomenon has not been described in pulmonary infections due to gram-negative bacilli. Ten separate bacterial strains were isolated from the sputum of these 6 patients before streptomycin treatment was begun, and a significant increase in resistance to streptomycin occurred in 5 during or after the course of therapy. New strains of organisms not isolated before therapy were first obtained from cultures of the sputum during the course of streptomycin treatment in 2 cases. Both strains were also highly resistant to the action of the drug. The appearance of resistant bacteria during therapy may be an important factor in determining the eventual clinical results. In Case 6 streptomycin resistance developed rapidly, and there was no beneficial effect from the treatment.

In Case 3 there was a good clinical response initially, but a streptomycin-fast strain developed and the pulmonary infection became chronic.

The development of drug fastness by the infecting organisms, however, is not the sole factor in determining the clinical result. In 2 cases of bronchiectasis and in a severe case of pneumonia due to Friedländer bacillus there was marked symptomatic improvement despite the appearance of streptomycin-fast strains in sputum cultures. A third patient died of pneumonia caused by Friedländer bacillus during the course of therapy, and the strain recovered from the lung at autopsy was identical in its streptomycin sensitivity with the one obtained before treatment.

The basic conditions that give rise to the development of resistance are virtually unknown and it becomes difficult to understand why certain cases show the development of resistant strains and others do not. Two of these cases (Cases 2 and 3) were clinically and bacteriologically similar, and both had acute pulmonary infections that appeared to be similar in location and extent; the strains of Friedländer bacillus isolated in each case before treatment showed identical sensitivities to streptomycin by the method used, and the doses of streptomycin were comparable. Nevertheless, the Friedländer bacillus in Case 3 became streptomycin resistant, whereas a similar organism in Case 2 retained its original sensitivity.

Another point worth mentioning is the wide differences in sensitivity of strains of the same organisms isolated at different times after resistance had developed. This suggests that organisms of different resistance coexist in the same exudate and that, since single-colony cultures are tested, the sensitivity of the particular strain tested may be only a matter of chance.

It has been suggested that the maintenance of an alkaline reaction during treatment of urinary-tract infections enhances the antibiotic activity of streptomycin and thereby prevents or curtails the development of bacterial resistance.[14, 18] Offhand, it does not seem feasible to maintain an alkaline reaction in the infected tissues and exudate in pulmonary infections.

The mortality rate in pulmonary infections due to gram-negative bacilli is high even with the best forms of therapy. Bronchiectasis caused by gram-negative bacilli is often progressive and refractory to the usual antibiotic and chemotherapeutic treatment, and is not always amenable to surgery. Prolonged courses of sulfonamides and penicillin are helpful in some cases. Streptomycin, however, appears at present to be the therapy of choice in such cases, although as in the streptomycin treatment of other infections, clinical failures may result. Obviously, it cannot be expected that the structural damage in chronic cases will be repaired, but healing may be promoted by the reduction in or the elimination of the infection in such cases. In patients with abscesses or with large bronchiectatic cavities, streptomycin by inhalation preceded each time by postural drainage may be the method of choice when susceptible gram-negative bacilli are present in abundance. The inhalations should probably be supplemented by systemic therapy, particularly if there is an accompanying acute pneumonitis.

The favorable results in cases of pulmonary and meningeal infections with *H. influenzae* suggest a possible use of streptomycin in certain severe epidemics of virus influenza in which pulmonary infections are associated with that organism. There is reason to believe that most of the fatal pulmonary complications of epidemic influenza are due not to the virus alone but to its association with hemolytic streptococci, staphylococci, pneumococci and influenza bacilli. Penicillin and sulfonamides should prove effective in cases in which gram-positive cocci are involved, and streptomycin may fill the gap in those due to *H. influenzae*, which is only slightly — if at all — affected by the other agents.

Summary

Three cases of acute and 3 of chronic pulmonary infections caused by gram-negative bacilli are presented, and the clinical and bacteriologic results of treatment with streptomycin outlined. The results of therapy were favorable, although not uniformly so. One of the causes of clinical failure appears to be the rapid development of streptomycin resistance by the infecting organisms. In 1 case drainage from a chronic suppurative otitis media stopped promptly after systemic and local streptomycin therapy.

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SENSITIVITY TO PORK-LIVER EXTRACT IN PERNICIOUS ANEMIA*

Clinical Observations on Fourteen Patients

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NOT until several years after the classic report of Minot and Murphy[1] on the treatment of pernicious anemia with liver was a potent injectable liver extract first employed for the routine therapy of this disease. In 1933 Gänsslen[2] gave scant details of the method of preparation but described striking hematologic and clinical effects with the product later well known under the proprietary name of "Campolon." Subsequently, the cases of at least 175 patients who were sensitive to liver extract have been reported, half of them in the last three years. Individual studies indicate that such sensitivity is not a rare condition. Delikat[3] reported 14 cases, Feinberg, Alt and Young[4] recently reported 8 cases, McSorley and Davidson[5] encountered 40 cases in the past ten years, Kaufman, Farmer and Reich[6] reviewed 11 cases and Schwartz and Legere[7] observed 68 cases in 396 outpatients. In view of the number of recent reports, it is apparent that sensitivity is an important complication in patients receiving liver-extract therapy.

This report is based on 14 patients discovered in the past two and a half years to be sensitive to injections of liver extract. The total number of patients under observation during this period was about 200. The clinical manifestations of sensitivity exhibited by the patients can be divided into three varieties. The most frequent effect consisted of generalized itching, urticaria, edema of the face and lips, nausea and vomiting. The second type exhibited peripheral vascular collapse, including thready pulse, sweating, cyanosis, weakness and fainting. A third group of patients manifested local signs that may have been due to an Arthus type of sensitivity consisting of swelling, itching and induration without necrosis at the site of injection. Only one patient suffered from asthma. In all cases the immediate symptoms were relieved, at least in part, by the injection of adrenalin.

The maintenance of adequate parenteral therapy with liver extract in sensitive patients may be a difficult problem. In the cases discussed below, subsequent reactions were prevented by the employment of an injectable liver extract prepared from another animal source. This success occurred in many cases without complete correlation with the sensitivity as demonstrated by skin tests.

MATERIALS AND METHODS

The purified liver extract containing 15 *U. S. P.* units per cubic centimeter that had been routinely used in the treatment of patients who had become sensitized was prepared from pork liver, as are, apparently, the majority of liver extracts on the market at present. The injectable liver extracts employed for testing for sensitivity and administered subsequently by intramuscular injection were prepared from pork, beef and lamb and were of two potencies: crude (2 *U.S.P.* units per cubic centimeter) and purified (15 *U.S.P.* units per cubic centimeter).¶ For skin testing the extracts were diluted under sterile conditions with physiologic saline solution in the proportions of 1:100 and 1:1000. The special muscle extracts used for skin testing were made from pork, beef and lamb muscle. They were employed undiluted and also diluted with physiologic saline solution in a proportion of 1:10.

All skin tests were performed after the patients had developed sensitivity to pork-liver extract and during the course of therapy with beef-liver extract. They were done by the intracutaneous injection of

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TABLE 1. *Sensitivity to Various Substances as Demonstrated by Skin Tests.*

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Case No.	Purified Liver Extract*				Crude Liver Extract†						Allergenic Muscle Extract					
	Pork		Beef		Lamb		Pork		Beef		Lamb		Pork		Beef		Lamb
	1:1000	1:100	1:1000	1:100	1:1000	1:100	1:1000	1:100	1:1000	1:100	1:1000	1:100	1:10	undiluted	1:10	undiluted	1:10	undiluted
1	+++	++	0	0	0	0	+	++	0	++	0	0	−	0	−	0	−	0
2	++++	−	++++	−	++	−	+++	−	++++	−	+++	−	+++	+	+++	0	+	+
3	+++	++++	+	−	++	+++	++	−	+	−	++	−	−	++	−	00	+	+
4	−	++++	−	++	−	++	+++	−	−	−	−	−	−	−	−	+0	−	−
5	−	++++	−	0	+	−	−	−	−	−	−	−	−	0	−	0	−	−
6	+	++++	0	+	0	0	+	+++	0	++	0	00	−	00	−	+0	−	+
7	++	+++	0	0	0	0	+	−	0	−	+	0	−	0	−	0	−	+
10	−	++	0	−	0	++	+	+	−	−	+	−	−	−	−	−	−	−
11	−	+++	−	−	0	0	−	−	−	−	−	−	−	−	−	−	−	−
13	−	+++	0		0		−		−		−		−		−		−	

*15 *U. S. P.* units per cubic centimeter.
† 2 *U.S.P.* units per cubic centimeter.

TABLE 2. *Clinical Data in 14 Patients Sensitive to Liver Extract.*

Case No.	Age	Race	Sex	Diagnosis	Dosage of Pork-Liver Extract*	Injection before First Reaction	No. of Reactions	Clinical Signs of Sensitivity	Dosage of Beef-Liver Extract*	Frequency of Treatment	Remarks
	yr.				cc.				cc.		
1	60	W	F	Pernicious anemia	1 (monthly)	13	2	Collapse, vomiting, cyanosis and thready pulse	1 (monthly)	8 injections in 9 mo.	Beef-liver extract first given in small doses as a test
2	60	W	F	Pernicious anemia	1 (monthly)	4	1	Collapse, itching, nausea and vomiting	1 (monthly)	13 injections in 1 yr.	Sensitivity to beef liver manifested after thirteenth and fourteenth injections; oral route subsequently employed.
3	59	W	F	Pernicious anemia	1 (monthly)	7	4	Urticaria, itching and edema of lips	1 (monthly)	24 injections in 2½ yr.	Itching of palms after eighth injection of beef liver followed by desensitization and no further difficulty
4	32	W	F	Sprue	1 (monthly)	Many	Many	Edema and itching at site of injection	1 (twice monthly)	24 injections in 1 yr.	
5	41	W	F	Pernicious anemia	1 (monthly)	4	6	Nausea and vomiting	1 (monthly)	13 injections in 1 yr.	
6	41	W	F	Pernicious anemia	1 (monthly)	Many†	Many	Nausea, vomiting, general itching and itching at site of injection	1 (twice weekly)	5 injections weekly	Initial desensitization to beef liver without difficulty
7	68	W	F	Pernicious anemia	1 (monthly)	18	5	Flushing of face, nausea and urticaria	1 (monthly)	5 injections in 5 mo.	
8	53	W	F	Pernicious anemia	1 (monthly)	14	2	Flushing of face, itching and edema of lips	1 (monthly)	12 injections in 1 yr.	
9	57	W	F	Pernicious anemia	1 (monthly)	18	3	Urticaria, itching and edema of lips	1 (monthly)	20 injections in 1 yr.	
10	69	W	F	Pernicious anemia	1 (monthly)	12	1	Urticaria, itching and edema of lips	1 (monthly)	2 injections in 2 yr.	
11	34	N	F	Pernicious anemia	1 (monthly)	6	2	Urticaria and itching	1 (monthly)	17 injections in 2½ yr.	Itching after tenth injection of beef liver, followed by desensitization without further difficulty
12	78	W	M	Pernicious anemia	1 (monthly)	7	16	Edema of lips, followed by nausea and collapse	1 (monthly)	17 injections in 1½ yr.	
13	55	W	F	Pernicious anemia	Irregular	10	10	Urticaria, itching and edema of face	1 (four times weekly)	13 injections in 1 yr.	
14	55	W	F	Pernicious anemia	Irregular	18	2	Collapse, nausea, headache and asthma	1 (twice weekly)	Four injections in 2 wk.	

*15 *U.S.P.* units per cubic centimeter.
†Had received injections for more than four years.

from 0.01 to 0.02 cc. of the preparations mentioned above. Sterile physiologic saline solution was used as the control. Nearly all the skin tests were made by the same person and were read at intervals of five, ten, twenty and thirty minutes. The tests were interpreted as follows: o = negative (same as control); + = small regular wheal with slight erythema; ++ = moderate-sized wheal (up to 10 mm. in diameter) with definite erythema; +++ = irregular wheal over 10 mm. in diameter, without definite pseudopods but with definite erythema; and ++++ = large wheal with definite pseudopods and erythema. The results of the tests are presented in Table 1. The symbols given in the table represent the maximum reaction noted. Most authors agree that the presence of pseudopods constitutes a definitely positive skin test. On the basis of our criteria, however, both +++ and ++++ reactions were considered indicative of sensitivity.

Results

After four to eighteen or more monthly intramuscular injections, the 14 patients became sensitive to the purified extract containing 15 *U.S.P.* units per cubic centimeter and prepared from pork liver. The clinical information in these cases is summarized in Table 2.

None of the patients who became sensitive to liver extract prepared from pork experienced distressing symptoms when given an extract derived from beef liver. This change was made after reactions had occurred on one to eighteen occasions, or more, following the intramuscular administration of the commercial pork-liver extract. In 11 of the 14 cases (Cases 1, 4-10 and 12-14) this change in therapy completely — and so far, permanently — abolished all signs or symptoms of sensitivity. In Cases 3 and 11, however, after the eighth and tenth monthly injections of the beef-liver extract, respectively, itching of the palms occurred. Thereupon, both patients were desensitized by initially small (0.1 cc.) and gradually increasing (up to 1.0 cc.) weekly injections of the beef-liver extract. No further reactions occurred with subsequent monthly injections. Following the thirteenth injection, the patient in Case 2 experienced itching of the palms. She was apprehensive concerning another severe reaction and for this reason refused further injections. Consequently, desensitization was not possible. She is now being successfully treated with an orally administered liver extract prepared from pork. Two of the patients sensitive to pork-liver extract were given beef-liver extract initially in small doses, with an increase at weekly intervals to 1 cc. This was done as a further precaution, since the reactions to the pork-liver extract had been extremely severe.

The patient in Case 10, having been found sensitive to pork-liver extract and having been shifted to beef-liver extract, was subsequently given by error an injection of 1 cc. of a liver extract derived from pork. This was immediately followed by a severe reaction characterized by generalized itching, nausea, vomiting, feeble pulse and weakness. Treatment with beef-liver extract was subsequently resumed without difficulty.

The patients sensitive to liver extract prepared from pork who were skin tested, with one possible exception, exhibited greater sensitivity by this procedure to pork-liver extract than to extracts of beef or lamb liver (Table 1). The few skin tests with allergenic muscle extracts prepared from the same animal sources were negative or only questionably positive in most cases. In Case 6, although the patient was sensitive to pork-liver extract clinically and on the basis of skin tests, reactions with pork-muscle extracts were negative and those with lamb-muscle extracts were positive. In the other patients tested with the muscle extracts a greater sensitivity to pork muscle was observed.

It is difficult to correlate the clinical severity of the reactions with the results of the skin tests. Case 1 provided the most striking example of this discrepancy. In spite of severe reactions clinically, skin tests with pork-liver extract showed only moderately positive reactions. Only 1 patient (Case 6) gave a history of other allergic tendencies. She stated that she was unable to tolerate aspirin, codeine or barbiturates. She gave no history of asthma or hay fever.

As pointed out by many other investigators, the duration of therapy before symptoms of sensitivity appear varies tremendously. In the present series initial symptoms of sensitivity developed earliest after the fourth injection and at the latest after eighteen or possibly more injections over a period of years. The duration and the amount of treatment before the onset of reactions had no apparent relation to the severity of the symptoms.

Thirteen of the 14 patients included in this report were women. The frequency of liver-extract sensitivity among women has been observed by others. Kaufman, Farmer and Reich[6] reported that 70 per cent of all recorded cases had occurred in females.

Discussion

In treating patients with pernicious anemia who became sensitive to pork-liver extract, we were usually able to eliminate manifestations of sensitivity by changing the therapy to an extract derived from beef liver presumably by about the same method. This suggested that the sensitivity was of species-specific rather than organ-specific type, since the patients would otherwise have suffered further reactions when beef-liver extract was substituted for that derived from pork liver. The results of the skin tests in general confirmed this hypothesis. The majority of the patients showed a greater sensitivity to extracts of pork liver than to those of beef or lamb liver. Because of the rela-

tively weak reactions obtained with muscle extracts, we believe that no confirmatory evidence of species specificity can be derived from them.

There is a difference of opinion in the literature regarding the cause and nature of the sensitivity to intramuscular liver extract. In contrast to our experience, most authors favor Criep's[8] impression that the sensitivity is primarily of organ specificity, and all agree that it represents an acquired type of sensitivity. Criep based his conclusions on the fact that he obtained positive skin tests with liver extracts derived from hog, beef, sheep and chicken and negative tests when muscle extracts from the same animals were used. He believed that the sensitivity was to the liver proteins themselves. Andrews[9] suggested that the allergenic factor was the antianemic principle itself and that changing the animal source of the extract would not eliminate sensitivity reactions. Kaufman, Farmer and Reich[6] reported observations on 11 sensitive patients in whom the skin tests indicated that the sensitivity was to the organ and not to the animal. Feinberg, Alt and Young[4] concluded, in the 8 cases that they studied, that the sensitivity was to a special organ fraction associated with the antianemic factor. They reported a patient, however, who was able to tolerate intramuscular injections of beef-liver extract but not of extract derived from pork liver. Engelhardt and Derbes[10] suggested that reactions in some cases were due to impurities but that in general the sensitivity was to the organ and not to the animal from which the extract had been prepared.

On the other hand, there is evidence in the literature to support our conclusion that biologic specificity is a significant — if not the most important — factor in sensitivity to liver extract. Rynes and Tocantins,[11] in an excellent review of the literature on sensitivity to liver extract, presented the case of a patient who was able to tolerate beef liver extract but when given pork-liver extract exhibited an Arthus type of sensitivity. Nausea was induced when this patient was given pork to eat. Skin tests, however, were positive for liver and muscle extracts of pork, beef and lamb. The authors concluded that the cases represented a biologic type of sensitivity. In 2 cases reported by Jones[12] 1 patient tolerated without difficulty intramuscular injections of liver extract prepared from beef but reacted severely to an extract of pork origin. Skin tests, however, as in our Case 2, indicated that the patient was sensitive to both liver extracts. Later, the patient was given a horse-liver extract without difficulty. In a patient reported by Bynum,[13] sensitivity first appeared after eleven injections of an extract, Reticulogen (Lilly), stated to be prepared from pork. The patient tolerated without difficulty injections of an extract derived from beef liver.

Most authors who explain liver-extract sensitivity by organ specificity base their conclusions on the results of skin tests with liver and muscle extracts. From an analysis of the cases included in this report, it is evident that the change in therapy to an extract from a different animal source resulted in the abolition of sensitivity symptoms regardless of the results of the skin tests. Sensitization to liver extracts derived from pork rather than from beef liver predominates in all probability because most of the commercial extracts used in this country are derived from pork liver. Certainly, some persons may have an organ-specific sensitivity, but no such cases were encountered in our series.

Summary

Fourteen cases of acquired sensitivity to a pork-liver extract given intramuscularly are reported. Symptoms of sensitivity were abolished by a change of the therapy to an extract derived from beef liver.

Skin tests with liver extracts derived from pork, beef and lamb indicated in general greater sensitivity to extract of pork liver than to that of beef and lamb liver.

In the cases studied, clinical experience consistently — and skin tests to some extent — indicated that the sensitivity to liver extract represented an acquired type of species rather than one of organ specificity.

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THE COMMONWEALTH'S HEALTH PROGRAM

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GOOD health has always been one of man's most prized possessions. From the most primitive times he has endeavored to take advantage of such knowledge as was available to him in prolonging his life, in preventing disability and in avoiding sickness. Believing that disease was of demonic origin he employed various mystic incantations in an attempt to ward off and to cure illness. The Mosaic laws contain the first rudimentary development of a definite sanitary code. Not until relatively modern times, however, could advantage be taken of accurate scientific knowledge in the prevention of disease, the prolongation of life and the attainment of optimal health.

Massachusetts has always been one of the pioneers in the field of public health. About two hundred years ago, Boston passed its first ordinance for the purpose of quarantining ships entering the harbor from ports where diseases such as yellow fever and smallpox were prevalent. Approximately twenty-five years later, the ubiquitous Paul Revere, who not only completed his famous ride but also made George Washington's false teeth, became chairman of Boston's first board of health. In 1869 the first state department of health in this country was created in Massachusetts. Since then, official health departments have been extended throughout the entire country.

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In medical care, Massachusetts has also taken the lead and has supported certain phases of so-called "state medicine" for over a hundred years. At present there are no less than seven departments of the state government taking an important role in medical care. Of primary significance are the boards of registration that, through the licensing of doctors, dentists, pharmacists and nurses, attempt to ensure quality in medical practice. Unless there are adequate standards for practitioners, there cannot be adequate medical care. Although the Approving Authority for medical schools has now made it impossible for graduates of unapproved schools to take examination for licensure in the Commonwealth, it must be remembered that, in Massachusetts, approximately fifteen hundred graduates of substandard schools are at present engaged in active practice.

Two groups are interested in the medical care of the worker in industry. The Industrial Accident Board is concerned with the medical and hospital care of workers injured on the job, whereas the Division of Occupational Hygiene in the Department of Labor and Industries studies the health hazards that the worker encounters.

The Department of Public Welfare not only maintains the State Infirmary at Tewksbury and the Massachusetts Hospital School at Canton for the custodial care of crippled and deformed children but also finances the medical care of indigent persons suffering from diseases that are not communicable. The Vocational Rehabilitation Program, under which any person of legal employable age who is totally or partially incapacitated for remunerative occupation may obtain assistance, is administered by the Department of Education. In case of financial need, the corrective medical, surgical or psychiatric treatment required to make it possible for the patient to obtain employment is provided. For example, if a man has a hernia that interferes with his ability to work, he may have it repaired. The Department of Mental Health, which has perhaps the largest financial stake in medical care, provides treatment for the mentally ill and the mentally defective in its various institutions.

The last group concerned is the Department of Public Health, which, almost from its inception, has had a considerable stake in the problem of medical care. The first tuberculosis and cancer hospitals to be maintained at state expense were started in Massachusetts. Hospitalization of tuberculous patients is recognized as an integral part of a tuberculosis-control program. Immediate care is essential. If "red tape" holds up the hospitalization of a patient with tuberculosis, the chances of its spread among contacts is increased, and the likelihood of recovery is materially reduced. It is a well known fact that 85 per cent of tuberculosis cases can be arrested if treated in time. A major problem in the care of tuberculous wage earners is that frequently no provision is made to assure an adequate standard of living for their families. Steps are now being taken, however, to correct this deficiency.

State sanatoriums for the treatment of cancer patients are provided at Pondville and Westfield. The Department of Public Health also maintains twenty co-operative cancer clinics, at which the physicians give their services without compensation. These are essentially diagnostic clinics, since no operations are performed and no extensive radiotherapy is given. As in cases of tuberculosis and other communicable diseases, immediate care is vital. Experience has shown that the disease can

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often be cured, or at least arrested, if treated in time.

The Commonwealth has assumed responsibility for the care of cases of communicable disease for over half a century. Automatically, as soon as the Department of Public Health declares a disease to be dangerous to the public health, the local board of health becomes responsible for the care of the patient, provided he is unable to pay for treatment himself. If the patient with a communicable disease is a state settled case, he becomes the responsibility of the Department of Public Welfare. The local boards of health and of welfare have been giving medical care on the local level for many years.

The Department of Public Health also furnishes treatment for cases of venereal disease. It maintains twenty-five clinics, which co-operate with the local hospitals. Moreover, free transportation is furnished, if necessary. It provides specific drugs,including the sulfonamides, free of charge to private practitioners for the treatment of venereal diseases, but the physician must be remunerated by the patient for the services he renders; penicillin is furnished without cost to the Co-operating Venereal Disease Clinics.

Another series of clinics that the Department of Public Health sponsors are those for crippled children. These clinics care for any child whose family cannot afford the expensive and long-continued medical treatment necessitated by his crippled condition. All such cases are referred by the family physician or some social agency. A new project is now under way for the care of patients with rheumatic fever. Facilities that have been made available at the North Reading State Sanatorium will make it possible to proceed as soon as adequate personnel is available.

The Commonwealth has been reasonably successful in controlling infectious diseases. In the days of Paul Revere the normal life expectancy was thirty-five years. Today it is sixty-five, and in the near future it will probably be extended to seventy-five. Not much has been accomplished, however, in the care of the chronically ill. Plans are being drawn up for a new chronic-disease hospital at Stoneham, which will accept three types of patients: those in need of hospitalization; those whose treatment will contribute to knowledge of the disease and of methods for diagnosis and treatment; and those with cases that will furnish instruction for doctors and students in the various aspects of the disease. This will not be a custodial institution, but every effort will be made to get the patient on his feet so that he may be discharged. There will also be a large outpatient clinic. Patients will be admitted to this hospital under the same conditions as those governing the admission of cancer patients, few of whom pay any part of their expenses.

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Public health has made outstanding progress in the prevention of disease, and in the phases of medical care mentioned above. In spite of the fact, however, that well administered health departments are an accepted part of state government, approximately a third of the nation's population are actually living in communities not covered by public-health services. Thus, many citizens of the Commonwealth are deprived of the benefits of the latest developments of medical science and preventive medicine. One of the major problems in Massachusetts is the establishment of adequate local health facilities for all the people. Only by the provision of such facilities under the direction of a full-time, trained and experienced health officer can the citizens of any area attain the greatest benefits from sanitation, prevention of communicable diseases, adequate nutrition and all the other factors that ultimately, in their full utilization, bring about the achievement of optimal health. The national welfare demands that the people in small towns receive the same benefits as those in large cities.

Perhaps a definition of the term "optimal health" should be given. If a person is enabled to develop his physical and mental health to the highest degree and to maintain them at high level, he has achieved optimal health — in other words, he is given the opportunity to develop and to utilize the potentials with which Nature has endowed him so as to obtain satisfaction from life and to contribute the greatest effort to the community. Optimal health, therefore, is the summation of the achievements in all spheres of the medical sciences and the healing arts that bring about the greatest happiness, the greatest utilization of one's abilities, the longest life span and the greatest good to the individual, his family and his community.

The responsibility for making available these benefits of medical science and the healing arts rests first with the family, secondly with the official community agencies and thirdly with the voluntary agencies. The health of a person is essentially his responsibility — only if he neglects his health or if his illness adversely affects the community in which he lives does he become a problem of the community. Leaders in the field of public health believe in the rights of individuals. They believe that medical care is a man's own responsibility, just as his family is his responsibility; he should provide such care if he able to do so. Neglect of his health may be due to carelessness and to lack of consideration for his family and his neighbors or to inability to obtain adequate means of prevention or of treatment. Whenever an illness affects other members of the community, health is no longer a purely personal problem but becomes the responsibility of the community as well. The provision of medical care for a patient who has scarlet fever is a family obligation, but his isolation and the quarantine of his contacts are the responsibility of the community. If the family is unable to provide adequate care, the community must meet the need.

Similarly, the patient who is ill with a disease such as diabetes or cancer is primarily responsible for his own care. If he neglects his own health, however, either wilfully or because of lack of means, and becomes a burden on the community in that he is no longer self-supporting and his dependents are potential welfare charges, the health of the patient becomes the concern of the community. It assumes the responsibility for his care, so that he will not remain a continued liability but will again become an asset — independent, self-supporting and contributing to the public welfare.

Under the Constitution of the United States, the responsibility for the health and welfare of the people rests officially with the state and not with the federal government. The state may delegate this responsibility to its political subdivisions. In Massachusetts, the responsibility has been delegated to the state and local boards of health and of public welfare. Although there is an excellent health department on the state level, health departments have failed to provide the people with adequate health services on the local level. The provision of adequate health service, which is now a primary responsibility of health departments, can be attained only through the organization of permanent town unions. Each union should include about 30,000 people to provide for the employment of full-time, trained health workers. Since a minimum of approximately $2.00 per capita is required for efficient health administration, a subsidy must be made available to these health departments from the state government. The local health department should be administered by a full-time physician not engaged in private practice. He should be advised by a board of health that has no executive authority. School health programs should be an integral part of the health department's function and closely co-ordinated with the other health activities.

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The voluntary agency has a vital role in community health organization. Often, in our complex civilization, the official agency does not furnish all the facilities necessary to render complete and adequate care of the needy. The voluntary health agency can and should assume some of the burden by providing for the care of such groups of patients as are not included under the functions of the official agencies and by disseminating knowledge and promoting programs that increase the community's assets for the attainment of optimal health.

The voluntary health movement in the United States began about sixty years ago with the formation of the Pennsylvania Society for the Prevention of Tuberculosis. At that time this was an extraordinarily far-sighted step — one that was so far in advance of the times that it was not duplicated in other states for over ten years. A second state society was organized in Ohio in 1901, and a third in New York in 1902. The National Tuberculosis Association was formed in 1904 and included twenty-three state and local organizations. These have increased to such an extent that at the present time there are over three thousand chapters in the United States. The most striking fact is the marked unevenness of the voluntary movement. There are over twenty thousand voluntary health agencies — some excellent, but others inadequate. Because it developed spontaneously to meet newly recognized needs in a variety of neglected fields, the movement has lacked over-all direction and planning. The time is ripe for stocktaking and for developing sounder programs. Many of the present activities of volunteer societies should properly be absorbed by the official health departments, which, after all, are the responsible health agencies. There is therefore a need for increasing the co-ordination of effort on national, state and local levels. In fact some authorities have advocated the unification in one strong organization of all the related health-promoting voluntary agencies in a city or in a state, with appropriate emphasis on the various aspects of a unified health program. Such authorities as Gunn and Platt[1] recommend "the pooling of the present separate competitive and confusing appeals of the voluntary national health agencies into a unified nationwide campaign effective on the local, state and national levels, along the lines already proved to be acceptable to the American people through the National War Fund in conjunction with the community chests."

On the other hand, certain groups are interested in promoting a compulsory health program administered by the federal government that would, to a large extent, sound the death knell of many of the voluntary health agencies. Even if the eventual taking over of all the technical services for public health by official agencies could be visualized, four important functions of the voluntary public-health agencies would remain.

In the first place they would remain the guardian and watchdog of the official health department. Voluntary organizations of alert and informed citizens, sensitive to the community's need in public health, can serve at all times to defend, strengthen, criticize, support and assist the official agency as a servant of the public. Such organizations would always take an active interest in promoting health legislation in all levels of government. They are needed, especially if national in scope, to stimulate and finance research. Finally, they have a continuing educational function. They can develop machinery for supplementing official health and educational organizations and can augment the efforts of professional groups to popularize scientific knowledge bearing on health.

Voluntary health agencies are here to stay. As Mustard[2] stated in a recent publication, "It requires only casual study of the situation to learn that a great deal of work important in maintaining public

health agencies is done outside the official governmental agencies."

In planning for the future the voluntary health agency must discover for itself how it can advance public health. Thus, such an organization has a definite responsibility to assist in making community surveys of existing institutions and of other facilities for the improvement of the health of the people. In promoting its own activities and functions an agency must be cognizant of the work of other agencies to avoid duplication and overlapping. Moreover, it is essential that all voluntary health agencies begin to co-ordinate their programs so as to discharge their responsibilities more efficiently.

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There are several immediate needs for public-health programs in Massachusetts. The first of these is the strengthening of the official agencies — namely, the state and local departments of health. A health department must be able to function free of political interference if it is to carry on its duties efficiently and on the basis of scientific knowledge. Thus, the health commissioners should be appointed by the Public Health Council rather than by the governor or the mayor of a city. They should be assured of some security of tenure and should not be subject to the turnovers that often follow a change in political regime. They should likewise be assured of reasonable compensation — one that would provide them with a standard of living equal to that of other leaders in medical practice in their communities. Their staffs should have similar protection, and whenever possible they should be protected by Civil Service laws and should receive higher compensation than that received at the present time by practically all health department employees in the Commonwealth. As a matter of fact, in many health departments, there is a dearth of physicians and other professional personnel because of the comparatively low salaries paid these employees. It is therefore necessary that the Massachusetts Medical Society and other professional groups lend their support to the common effort of raising salaries for health-department employees in the Commonwealth. The professional salaries of Massachusetts Department of Public Health personnel, which were set back in the 1920's, have not been changed, except for wartime increases. If state and local health departments are not able to obtain and to hold well trained personnel, the quality of public-health work will greatly depreciate, and this will enhance the politicians' opportunities to dispense jobs and federal grants not on merit but on any opportunity to favor his chances of re-election.

Local health departments must obtain adequately trained full-time personnel who do not engage in private practice and must form into town unions if they are to make available, to the citizens, the full benefits of the latest developments in public health. This calls for the unification of boards of health into a common board that would employ a full-time, specially trained public-health physician with an adequate staff of full-time professional assistants. The time is past when public-health administration can be considered a part-time activity or a field to which physicians who have conducted a full-time general practice can retire on reaching old age. To make possible the formation of town unions on a permanent basis, legislation at first permissive and later compulsory may be necessary. This should provide for a state subsidy, to be made available to town unions for the operation of such health departments. This is the procedure that is already effectively carried on in many states.

Voluntary health agencies should support the official health departments not only in the obtaining of more adequate funds but also in the passage of proper legislation and in the strengthening of the departments that are sorely in need of adequate personnel and facilities. In the past, voluntary health agencies, by passive acquiescence rather than by active support, have often gone along with health departments and have not assumed their proper share of the responsibility.

Doctors, nurses, other professional workers, lawyers, bankers, civic leaders and representatives of all groups interested in health should band together and form community health councils. These councils not only should survey their communities to determine the facilities that are available for health and medical care but also should ascertain the needs of the communities and assist in formulating plans to meet such needs. The health councils should also co-ordinate the work of the various agencies, assist in the avoidance of duplication and help in the provision of more complete coverage most efficiently to expend the public funds collected through either taxation or voluntary contribution. Finally, community health councils, working with the assistance of the medical profession and health department, should develop continuous health education programs, designed not only to keep the public informed on health matters but also to obtain public support for health programs.

By the strengthening of the official health agency, by obtaining health departments free from political interference, by providing personnel adequately trained, secure in office and properly compensated, by co-ordinating the work of all the voluntary health agencies and by receiving the support of the public, professional groups and civic leaders, public health in Massachusetts can attain the desired objective of all those interested in the health and welfare of the people — namely, optimal health. Only by this concerted and continued active support of all interested can this goal of optimal health be attained.

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MEDICAL PROGRESS

UROLOGY

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THE following is a review of recent studies on the use of streptomycin in urologic infections, testicular neoplasms, retroperitoneal tumors and necrotizing renal papillitis.

STREPTOMYCIN

Considerable progress has been made in recent years in ability to control infections of the urinary tract. Mandelic acid, the sulfonamides and penicillin have played a role in the problem, and during the past year another preparation has become available for this purpose. In 1944 Schatz, Bugie and Waksman[1] first described the isolation of a new antibiotic agent that they named "streptomycin." Animal experiments demonstrated the low toxicity of this agent and its effectiveness against infections due to gram-negative bacilli.[2-5] Since any one of these preparations is chiefly effective against certain groups of bacteria, or even strains of bacteria, the value of the identification of the infecting organism has become increasingly clear. The sensitivity of the bacteria to the therapeutic agent has also become an important consideration.

The method of preparation and directions for the administration of streptomycin are given in a report of the Committee on Chemotherapeutics and Other Agents of the National Research Council.[6] Streptomycin is available as the sulfate salt or the hydrochloride salt. Both salts are readily dissolved in distilled water or isotonic sodium chloride solution. Concentrations of 100 to 175 mg. of streptomycin per cubic centimeter of solution are prepared for intramuscular injection. Enough solution should be used so that the preparation is clear and free of undissolved particles. The total volume should be as small as possible. The expiration date of vials of streptomycin is eighteen months after release. The drug should be kept in the refrigerator. Intramuscular injection is the method generally employed for urinary-tract infections. Maximum serum levels of streptomycin are reached within one to three hours after intramuscular injection, and additive effects are obtained by a repetition of the dose every three or four hours. Most of the streptomycin is excreted from the blood into the urine by the kidneys.

Four hundred and nine cases of infection of the urinary tract are included in the report by the Committee on Chemotherapeutics and Other Agents. All cases were resistant to the sulfonamides, and many varieties of bacteria were represented. Most of the patients were given daily intramuscular injections of solutions containing 1 or 2 gm. of streptomycin for five to seven days, with an average total dose of 7.5 to 10 gm. Many infections were of long standing. The over-all recovery rate in this series was 42 per cent. It was concluded that it was difficult to assess the relative merits of streptomycin in this group of infections, but many of the patients were improved, without recurrences. Mixed infections did not respond so well as those due to a single organism. A rapid development of resistance by bacteria to streptomycin was observed, and it was thought that this accounted for many cases of failure to sterilize the urine. The favorable effect of streptomycin on infections due to *Proteus vulgaris* in this series should be noted.

A rapid increase in resistance to streptomycin by organisms infecting the urinary tract appears to be a major problem, and this fact merits careful consideration in the future treatment of patients with such infections. Sensitivity tests in vitro seem a reasonable guide to treatment. The rapidity with which organisms can acquire resistance to streptomycin is emphasized in a report from the Boston City Hospital by Finland et al.[7] and by others.[8,9] The former showed that in 8 carefully observed cases of urinary-tract infection a considerable degree of resistance to streptomycin was acquired by the infecting organisms within a short time. Repeated tests of organisms isolated before treatment showed them to be sensitive in vitro, whereas those obtained after treatment were highly resistant and the patients failed to respond to apparently adequate doses of streptomycin. It has been stated that dosage should be guided by the sensitivity of the organism and that, when possible, an adequate concentration of streptomycin should be maintained in the blood and tissues to inhibit the growth of organisms.[6] It was thought that in this way the resistance to streptomycin could be reduced. For urinary-tract infections a daily dose of 1 to 3 gm. for five to ten days was recommended.[6]

Streptomycin is most effective in an alkaline medium. This fact was observed by Schatz, Bugie and Waksman[1] and confirmed by Abraham and Duthie.[10] Differences as great as tenfold were encountered between activities measured at reactions of pH 6.0 and pH 8.0. The reverse was true of

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penicillin, an acid substance. The explanation was that the ionized forms of the basic drugs (streptomycin) compete with the hydrogen ions, and those of the acid drugs (penicillin) compete with hydroxyl ions, for position on the cell surface. Since tissue damage is accompanied by an increase in the local acidity, a concentration of a basic drug, such as streptomycin, that is effective in blood may be inadequate to destroy bacteria in local lesions.

The importance of alkalinization of the urine during streptomycin therapy is brought out in a recent report by Kane and Foley[11] presenting the results of treatment in 38 cases of pyelonephritis and 2 cases of cystitis due to gram-negative bacilli. Most of the patients had previously been treated with sulfonamides, mandelic acid and penicillin. The duration of the infection in each case had varied from weeks to years. Seventy-five per cent of patients were cured, and 10 per cent showed improvement. It is noteworthy that several of the cured patients had small renal calculi, and others had moderate structural deformities. The failure in 15 per cent could be attributed in each case to the fact either that marked structural deformity was present or that the concentration of streptomycin necessary to inhibit the growth of the infecting organism was higher than could be obtained in the urine with the dosage employed. The authors attribute the more favorable results obtained in their series, as compared with those of others, to the fact that the urine in each case was rendered alkaline during therapy.

Certain toxic reactions may occur during treatment with streptomycin. These are chiefly sensitization reactions with skin eruptions and fever, vertigo and tinnitus.[6] If a skin rash appears, it is advisable to stop streptomycin or continue treatment with care. In patients on prolonged courses of streptomycin, vertigo has been the most troublesome symptom, but many patients apparently overcome the subjective symptoms in spite of continued treatment. Tinnitus is considered a warning signal to decrease the dosage.

Although the streptomycin therapy of certain pyogenic infections of the urinary tract has been given at least a moderate trial and appears to be effective in many cases, particularly those due to gram-negative bacilli, its usefulness in renal tuberculosis is less clearly defined. This is because it soon became evident that long courses of treatment were necessary and supplies of streptomycin were limited. There is some evidence, however, that streptomycin is helpful in this disease. The results in 12 patients with genitourinary tuberculosis treated with streptomycin at the Mayo Clinic were sufficiently encouraging to make further trial interesting.[12] Although the patients were probably not treated for sufficiently long periods, a temporary beneficial effect was obtained in a reasonable number of cases. Pyuria was decreased, vesical symptoms were improved in some and the number of tubercle bacilli in the urine was said to have decreased. Bladder ulcerations healed in a case of renal infection treated over a long period and reported by Alyea.[13] There are no reports of streptomycin therapy in cases of early renal tuberculosis.

Testicular Neoplasms

Hormonal tests for the diagnosis and prognosis of testicular neoplasms were in general use ten or twelve years ago. Indeed, a classification of these tumors was advocated at one time on the basis of quantitative determinations of the gonadotropic hormone in the urine.[14, 15] These tests have been largely abandoned because of inconsistent results. Embryonal carcinomas, teratomas and seminomas — all of them malignant — frequently gave negative tests before operation. It soon became evident, moreover, that the tests did not always provide an accurate index of the subsequent course of the disease. Many patients with advanced metastatic lesions gave negative tests.

Brewer[16] recently reported 2 cases of primary testicular neoplasms. The histologic diagnosis in one was teratoma, and in the other, seminoma. The metastases in both cases, however, were chorioepitheliomas. When each patient was first seen tests for chorionic gonadotropin in the urine (Friedman and Aschheim–Zondek tests) were positive. It was believed that although chorionic tissue had not been demonstrated histologically in the primary tumor, it must have been present, since chorionic gonadotropin was present in the urine and the metastases were chorioepitheliomas. Small areas of chorioepithelioma may have been present in the primary tumor but not detected on microscopic examination because the entire tumor was not examined or because it may be difficult to differentiate chorionic tissue from the varied tissues composing a testicular neoplasm.

That two distinct types of gonadotropin reactions occur in tests with testicular tumors is pointed out by Brewer. These reactions represent two different gonadotropic hormones. One is the chorionic type of gonadotropin, identical with that formed in the urine of pregnant women; it produces luteinization in the ovarian follicles of test animals. The second type of gonadotropin is the castrate type elaborated in the pituitary gland. This hormone is present in the urine of male or female castrates, in women past the menopause and in elderly men. It produces follicle growth but not luteinization in the ovaries of test animals.

It is necessary to distinguish between these two reactions when testing for tumors of the testis, and failure to do so has caused confusion in the correlation of the test and the type of tumor. Brewer considers the presence of chorionic gonadotropin in the urine to indicate the presence of a biologically active tissue, whereas the presence of castrate type of gonadotropin means merely a reduction or cessation

of testicular function. As applied to testicular tumors, then, the chorionic gonadotropin is the more important hormone, and its presence in the urine is detected by the usual tests of pregnancy.

The results of orchidectomy and external irradiation in 80 cases of malignant testicular neoplasm by Nesbit and Lynn[17] give a survival rate of 24 per cent. The patients were followed for a minimum of four years. It is pointed out that an occasional patient of this sort with metastases has survived long enough to be fairly regarded as cured. Two patients with proved metastases have lived for eleven and twelve years following treatment, with no evidence of recurrence. Four patients lived from four to six years and then died of the disease, so that any study based on a four-year follow-up is considered subject to approximately a 10 per cent error. Only about a third of the cases reported by Nesbit and Lynn showed a significant elevation in prolan level. Removal of the tumor and postoperative — not preoperative — irradiation are favored by the authors.

A surprisingly high incidence of testicular tumors was found in the armed forces. Vermooten[18] attributed this to the easier access to medical advice, frequent examinations and the rigors of training. He explained the low incidence of metastases by the earlier diagnosis made possible because of these facts. Others, however, reported a high incidence of metastasis (24 per cent) among soldiers when first seen with testicular neoplasms and discouraging results after treatment.[19] No correlation was demonstrable between the results and the duration of the disease before treatment or the type of tumor.

From 1940 to 1946 the Army Institute of Pathology collected 922 cases of tumor of the testis from Army patients.[20] Over 96 per cent of these neoplasms fell into the following classifications: seminoma (germinoma), 35 per cent; embryonal carcinoma, 19 per cent, and chorioepithelioma, 0.4 per cent; teratoma, 7 per cent; and teratocarcinoma, 35 per cent. Clinically as well as histologically the seminomas were less malignant than the embryonal carcinomas, and the authors expressed the opinion that these tumors differ not only in fundamental cell type but also in biologic behavior and prognosis.

Fully differentiated chorioepitheliomatous tissue was present in about 6 per cent of embryonal carcinomas, and the hemorrhagic necrosis and vascular invasion characteristic of chorioepitheliomas were frequently seen in the embryonal carcinomas. Pure primary chorioepitheliomas accounted for less than 0.4 per cent of the tumors. The fact that chorionic gonadotropin is often present in the urine of patients with so-called "embryonal adenocarcinoma" is considered to provide physiologic substantiation for the morphologic observation that many embryonal carcinomas are trophoblastic tumors. The new term "teratocarcinoma" is proposed to include the large group of pleomorphic tumors in which both differentiated teratoid structures and histologically malignant elements are present.

An interesting feature of this group of tumors was that the death rate and incidence of metastasis were practically the same for the adult teratomas and the teratocarcinomas, supposedly because a teratocarcinoma matured into an adult teratoma after malignant embryonal cells had already been disseminated to other parts of the body. A study of the histologic components of the primary tumor and the metastases showed that 90 per cent of the embryonal carcinomas metastasized as embryonal carcinomas or chorioepitheliomas and that 40 per cent of the metastases of teratocarcinomas were embryonal carcinomas or chorioepitheliomas. It therefore appears obvious that any of these tumors may display chorioepitheliomatous tissue in their secondary deposits. Whereas only 0.4 per cent of these tumors were pure chorioepitheliomas, 27 per cent of all the metastases in cases that terminated fatally contained chorioepithelial elements. This excellent report deserves the attention of all who are interested in tumors of the testis.

In a study of testicular neoplasms in dogs Huggins and Pazos[21] found that atrophy of the prostate was present in all tumors except the interstitial-cell variety, in which the prostate was normal or enlarged. The authors present evidence that the interstitial-cell tumors arose from the Leydig cells and that the tubular adenomas originated from the cells of Sertoli. They also confirmed previous observations that seminomas arose from the germinal epithelium.

Most of the recent reports on tumors of the testis emphasize what has long been regarded as an important feature in their management. This is ligation of the spermatic cord high in the inguinal canal and removal of the affected scrotal contents through this incision without opening the tunica vaginalis. This procedure lessens the likelihood of local recurrence from tumor-cell implantation. In a recent case of a highly malignant testicular tumor in our own experience, the hydrocele fluid associated with the neoplasm was found to contain many tumor cells in the stained smear.

Retroperitoneal Tumors

Tumors that arise independently in the retroperitoneal tissues are not frequent but are of considerable interest. This group of neoplasms concerns both the general surgeon and the urologist, since the outstanding sign is often an unexplained abdominal mass, and the close relation of the mass to the kidneys and ureters is apt to deform or displace these organs. Past references concerning primary retroperitoneal tumors have not been complete. All the available information about these tumors is presented by Donnelly,[22] with a report of 95 cases observed during the past twenty years at the University of Iowa Hospitals.

The retroperitoneal space is described as between the lumbar and iliac regions and between the peritoneum and the posterior parietal walls of the abdominal cavity. The tumors originate within this space behind the posterior peritoneum. They may take origin from the urogenital ridge, fatty or connective tissue, lymphatic vessels or sympathetic nervous tissue. As they enlarge, they displace the abdominal viscera and may involve the mesentery of the large or small bowel. The tumors may be benign or malignant and occur at any age. The wide diversity of cell types of retroperitoneal tumors was once explained on the basis that they arose from remnants of the urogenital apparatus.[23]

Primary retroperitoneal neoplasms have varied considerably histologically. Sarcomas were regarded as the most frequent of the malignant tumors and lipomas as the most frequent of the benign types. The nonmalignant tumors are said to be potentially malignant and prone to recur. Even the lipomas, when they occur retroperitoneally, have a tendency to undergo malignant change, with recurrence and death. This tendency to recur is also true of other usually benign tumors when retroperitoneal — namely, fibromas and leiomyomas. The explanations given for this fact are that small outgrowths of these tumors are overlooked and not removed at operation and that the tumors contain sarcomatous elements not readily identified histologically.

Retroperitoneal cysts represent a type of these tumors. They have been classified as cysts of urogenital origin, teratomatous cysts and lymphatic, traumatic and parasitic cysts. They are most frequent in women from fifteen to twenty-five years of age and usually occur on the left side. The preoperative diagnosis is apt to be ovarian cyst.[24]

Of the 95 cases of primary retroperitoneal tumors in Donnelly's[22] series 82 were classified as malignant, and 13 as benign. Sarcoma, fibrosarcoma and undifferentiated neoplasms, such as embryoma and adenocarcinoma, were the most frequent, accounting for 81 per cent of the malignant tumors. Epithelial cysts were the most frequent benign tumors.

Gastrointestinal symptoms predominated in the patients with retroperitoneal neoplasms. Indefinite abdominal pain in the lower abdomen, nausea, constipation and anorexia were the usual complaints. Some patients noted the presence of an abdominal mass. As the mass increases in size, the symptoms are those resulting from pressure on adjacent structures. Symptoms had averaged over nine months before these patients sought treatment.

Patients with retroperitoneal tumors usually presented diagnostic problems. Gastrointestinal x-ray films and retrograde pyelograms assisted in the making of a correct diagnosis before operation. When these steps had been omitted the preoperative diagnosis had usually been ovarian tumor in the women and cancer of the gastrointestinal tract in men.

The treatment of these tumors is exploratory abdominal operation with removal of the tumor mass if possible. Eighty-two of the patients in this series were operated on. Forty-eight, or 65 per cent, were found unsuitable for surgical removal. Twenty-eight patients received deep x-ray treatment, and 77 per cent of the tumors were considered radiosensitive. Best results were obtained when complete surgical excision of the tumor was possible. An operative mortality of 20 per cent indicates the hazard of surgery in patients with primary retroperitoneal tumors.

Necrotizing Renal Papillitis

An interesting and usually fatal type of suppurative pyelonephritis that is frequently, but not always, associated with diabetes is described by Robbins, Mallory and Kinney.[25] The pathologic characteristics of this condition are abscesses in the renal pyramids with sufficient extension to cause necrosis of the terminal portion and suppuration and gangrene of the renal papillae. In most of the cases death was directly attributable to a necrotizing papillitis. Miscellaneous organisms are involved. Clinically this lesion should be suspected in severe, acute urinary-tract infections in diabetic and nondiabetic patients with urinary obstruction, particularly in the presence of oliguria and a rising nonprotein nitrogen. In the later stages of the disease pyelographic changes may be present.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33171

PRESENTATION OF CASE

A sixty-six-year-old Canadian housewife was admitted to the hospital for the fourth time because of recurrent pain in the right upper quadrant.

Two years before admission occasional attacks of sharp pain in the right upper quadrant had begun, sometimes originating at about the anterior axillary line and radiating to the epigastrium and substernal region. At other times the pain originated in the epigastrium and radiated to the right, along the lower costal margin to the infrascapular region. Radiation was also described as at times going into the right shoulder. These attacks recurred at monthly intervals and had become more frequent in the past year, sometimes only a few days apart. A year before admission a physician told the patient that she had gall-bladder trouble and started her on bile salts and a fat-free diet. She had been forced to call her physician frequently for the pains in the right upper quadrant, which were relieved by pills taken by mouth. At times these attacks of pain were associated with chills. During the attacks she became nauseated and sometimes vomited. She had considerable gas and had been constipated about a year, obtaining relief with mineral oil. About a month before admission her daughter noted that the patient had become yellow, but this had not increased in intensity and the patient thought that it had decreased. The stools had been clay colored but later were brown. She had been losing weight despite a fair appetite, falling from 220 pounds in 1936 to about 150 pounds at the time of admission.

The first admission to the hospital had been thirteen years previously because of a tumor in the right breast of five months' duration. This had proved to be carcinoma, and a radical mastectomy had been performed. The axillary lymph nodes were not involved. The patient did well until ten years later, when she again complained of tenderness and an indefinite tumor in the upper outer quadrant of the left breast, suggesting cystic disease. She was readmitted about eight months later, after considerable urging, and a left radical mastectomy was performed for another breast carcinoma. No involvement was seen in the axillary lymph nodes. About a year and a half after the second operation a firm oval nodule developed on the left that was slightly tender and adherent to the skin but not to the chest wall. This was excised and diagnosed as recurrent carcinoma. The patient then did well until six years before the present admission, when she noticed a small lump on the tip of the tongue. This increased slightly in size until all the teeth were extracted, when the lump began to decrease and subsided to the point where it was not necessary for her to return. Letters stated that she was well. A year prior to admission she had pneumonia and was confined to bed for three weeks at home and treated with sulfonamides and penicillin. She also stated that for the past twelve years she had had high blood pressure. Otherwise, she had no cardiac symptoms other than ankle edema in the evening, which had been present for about thirty years. She had also noted occasional palpitation and moderate exertional dyspnea.

Physical examination revealed a well developed, well nourished, slightly jaundiced woman lying quietly in bed in no acute discomfort. There was no evidence of recurrence in either of the mastectomy scars, and the chest was clear to percussion and auscultation. The heart did not appear to be notably enlarged. A Grade II, harsh systolic murmur was heard in both the apical and the aortic areas and transmitted to the neck, but the aortic second sound was not obliterated. There was no thrill. The abdomen was soft and obese, with moderate tenderness to pressure in the right upper quadrant in the midclavicular line, but no spasm and no masses. The liver was not palpated. There were minimal osteoarthritic changes of the distal phalanges of both hands. Over the ninth and tenth dorsal vertebras there was a subcutaneous, freely movable, nontender mass, measuring 3 by 3 cm., that was apparently a collection of adipose tissue.

The temperature, pulse and respirations were normal. The blood pressure was 220 systolic, 95 diastolic.

Examination of the blood disclosed a hemoglobin of 104 per cent and a white-cell count of 6250. The urine gave a ++ test for albumin, with a questionably positive test for bile. The stools were pale brown and guaiac positive. An electrocardiogram was described as showing sinus arrhythmia, with auricular premature beats, a rate of 46, a PR interval of 0.16 second, a QRS of 0.06 second, normal voltage, a tendency to left-axis deviation, a notched S_3, upright T waves in Leads 1, 2 and 3 and in Leads CF_2, CF_4 and CF_5 and slight sagging of the ST segment in Lead CF_5. X-ray studies of the chest and abdomen revealed no notable abnormality; no calculi were recognized in the abdomen. A bromsulfalein test revealed 28 per cent retention of the dye. The blood phosphorus was 3.7 mg., the nonprotein nitrogen 28 mg., the cholesterol 294 mg. and the cholesterol esters 130 mg. per 100 cc., and the alkaline phosphatase 20.9 Bodansky units. The prothrombin time was normal. A van den Bergh test was 1.6 mg. per 100 cc. direct and 2.2 mg. indirect. The total protein was 7.46 gm. per 100 cc., with an albumin-globulin ratio of 1.3. A cephalin-flocculation test was negative in twenty-four hours and ++ in forty-eight hours.

On the fourth hospital day a peritoneoscopy was negative. Two days later intravenous pyelograms and a barium enema were essentially negative. The liver was noted to be somewhat enlarged, slightly depressing the hepatic flexure. On the next day a gastrointestinal series revealed a 5-cm., sharply demarcated, nodular, tumor mass arising from the lateral aspect to the body of the stomach; a repeat bromsulfalein test revealed 20 per cent retention of the dye. On the twelfth hospital day a gastroscopy was performed, revealing a slightly atrophic antrum with a tightly closed, pale, normal pylorus. On the greater curvature, just proximal to the angulus, there was a nodular, polypoid, mulberry, reddish-purple, easily bleeding mass about 4 by 4 cm. in diameter and somewhat spherical in shape. It seemed to be wholly confined to the greater curvature. Toward the anterior wall the mucosa was pale, and numerous blood vessels were easily visible.

Two weeks after admission cholecystectomy was performed with exploration of the common duct. At operation multiple small calculi, measuring up to 8 mm. in diameter, were found in a chronically thickened gall bladder. The common duct measured 10 mm. in diameter and was explored without the finding of a stone. Two masses in the head of the pancreas were biopsied, and frozen section revealed chronic pancreatitis. The body and tail of the pancreas were irregular and nodular, the individual nodules measuring up to 20 mm. in diameter. None of these were thought by the surgeon to be typical of carcinoma. The gastric lesion measured roughly 5 cm. in diameter and was apparently attached to the greater curvature half way between the angulus and the cardiac end of the stomach. There were three small, tiny, lymphatic nodules and subserous lacteals in the greater curvature over the base of the tumor, but the lesion was thought to be resectable from the abdomen. On the day following cholecystectomy a bilateral prophylactic superficial-vein interruption was done, and about a month after admission a subtotal gastrectomy was performed.

Differential Diagnosis

Dr. Claude E. Welch: The first part of this history is a fairly definite story of gall-bladder disease, probably on the basis of common-duct stone, because of the repeated attacks and the fact that the common-duct obstruction had been intermittent in type, as evidenced by the stools. The only feature that we cannot explain well on the basis of gall-bladder disease is the rather marked loss in weight.

Dr. Fay assures me that these electrocardiograms are essentially normal.

This patient had some type of jaundice. The evidence points definitely toward obstruction of some type, as indicated by the high alkaline phosphatase. There is also evidence of a certain amount of liver damage as shown by retention of bromsulfalein, although it was not marked because of the normal prothrombin time. There were moderately elevated cholesterol and cholesterol ester levels, whereas the van den Bergh reaction showed evidence of slight jaundice. The flocculation tests were equivocal. All the heart studies, I should say, indicate that the patient was a good preoperative risk — almost anyone who walks around is a good risk, I understand. The x-ray film showed something that was not expected. May we see the film?

Dr. Richard Schatzki: Do you want to see the stomach film?

Dr. Welch: I want to spend more time on that than on anything else.

Dr. Schatzki: We have one film, not a spot film, on which the mass that was described can be seen.

Dr. Welch: Can you tell about the margins of the tumor?

Dr. Schatzki: From this film I assume that it was a polypoid mass in the lumen of the stomach.

Dr. Welch: You do not wish to say whether this area on the other side is normal?

Dr. Schatzki: In this film I think that I can see the upper edge of the mass. I cannot see the lower edge, which must be hidden by barium. On the plain film of the abdomen, the lower edge of the liver appears rather low laterally, but the liver edge is quite sloped and I do not dare to guess its size. I suspect, however, that the liver is a little enlarged, but with the liver edge so sloped as this, a moderately low liver does not mean much.

This is the intravenous pyelogram. The dye is not well concentrated, but I cannot see anything wrong with the kidneys.

The chest film shows the area of the missing breast on the left side, and there is no evidence of metastases.

DR. WELCH: The surgeon was faced with quite a problem: a known tumor of the stomach and a pathologic process in the biliary tract. Which should be attacked first, or should he be brave or foolhardy and attempt to do both at once? I assume that the wiser choice was taken in this case, because the patient had a low liver function and it was better to have the biliary tract functioning well before attempting gastric resection. The operation was probably done with the view of relieving the jaundice.

The empty common duct probably surprised the surgeon, and he undoubtedly explained it by saying that stones had passed through the common duct.

Many years ago, when Dr. Richard C. Cabot conducted these conferences, he put all his eggs in one basket and stated one diagnosis, which he made to cover all the findings. In these days, perhaps because the general incidence of older patients is so much higher, we consider ourselves lucky if we have such a thing as an uncomplicated carcinoma of the stomach. Obviously, in this patient it is impossible to make a single diagnosis to cover all the lesions. In the first place, the main problem that arises is that of the diagnosis of the stomach tumor, which may have been a primary tumor in the stomach, a recurrence of the carcinoma of the breast or a carcinoma of the pancreas that had been overlooked and had metastasized to the liver and to the stomach. The x-ray studies are helpful in that regard, because they rule out, for all practical purposes, any metastatic lesions. For an isolated metastasis to the stomach from carcinoma of the breast to show up six years after the last metastatic nodule had been observed would be queer indeed. Metastasis to the stomach from carcinoma of the pancreas is almost unknown, and a metastatic lesion of the stomach from either source that presented this x-ray picture would be impossible. We are therefore left with a discussion of the primary tumors of the stomach that can produce such an x-ray picture and give these findings by gastroscopy.

Before I saw this x-ray film I could not make up my mind regarding the exact type of tumor. Quite a list crossed my mind, such as fibrosarcoma, neurogenic sarcoma and leiomyosarcoma, all of which are frequent and produce spherical masses in the stomach, as well as an ectopic pancreas or lymphosarcoma. All these tumors were ruled out by the x-ray picture, which is not typical of any of them. We are restricted, practically speaking, to whether the lesion was a malignant polyp or a polypoid carcinoma. The gastroscopic picture does not help us a great deal in this regard. I should like to know whether any induration was noted around the base of the tumor, but I assume that there was none, since it would have been mentioned.

So far as the question of a gastric polyp or gastric carcinoma is concerned, Drs. Benedict and Allen* looked up these lesions many years ago. They found that 40 per cent of the entire group were carcinoma. The diagnosis perhaps could have been aided by a smear of the gastric sediment to determine if any abnormal cells were found. As it is, I shall have to guess that, because the tumor was large, the stools contained occult blood and the patient had lost a fair amount of weight, we are dealing with a carcinoma rather than with a polyp of the stomach.

My diagnoses are carcinoma of the stomach, gallstones and chronic pancreatitis.

DR. TRACY B. MALLORY: Dr. Robertson, will you give the opinion on the ward regarding the selection of procedures?

DR. CHARLES W. ROBERTSON: Dr. Welch went through exactly the same reasoning we did on the ward. The patient was a hypertensive woman with known obstructive jaundice and a gastric lesion. The x-ray film that we have here is, I believe, one of the later films that were taken between the two operations. On the first film of the stomach we were impressed by the nearness of the lesion to the cardia of the stomach and the possibility of mucosal extension of the tumor to the esophagus, and for that reason we seriously considered exploration through the chest. That is why the statement was made at the first operation that the tumor was resectable abdominally. The findings at the first operation were exactly as the record described them — namely, a chronic pancreatitis and a chronically inflamed gall bladder, with evidence that the patient had probably been passing small calculi. The jaundice cleared up quickly following drainage of the common duct. The stomach was then resected abdominally, two and a half weeks later.

CLINICAL DIAGNOSIS

Gastric carcinoma?

DR. WELCH'S DIAGNOSES

Carcinoma of stomach.
Cholelithiasis.
Chronic pancreatitis.

ANATOMICAL DIAGNOSES

Multiple polypoid carcinomas of stomach, with metastasis.
Chronic cholecystitis.
Chronic pancreatitis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: At the second operation a subtotal gastrectomy was done, and a large polypoid

*Benedict, E. B., and Allen, A. W. Adenomatous polypi of stomach. *Surg., Gynec. & Obst.* **58**:79, 1934.

tumor with central ulceration was found. To one side of that and separated from it by a strip of apparently normal-looking mucosa was a second polypoid tumor. Whether this represented two separate malignant lesions of the stomach or whether one was an extension of the other, it is impossible to say. It is quite possible that there were two separate tumors. Both were malignant histologically, and one or the other of them had led to a minute metastasis to a single lymph node, which we eventually found after sectioning a number of them.

DR. WELCH: An excellent reason for delaying the operation until after the biliary tract had been explored is the fact that polypoid carcinoma is relatively slow to metastasize.

DR. MALLORY: Dr. Schatzki, have you any further comment?

DR. SCHATZKI: So far as the tumors are concerned on the film, one can see only the upper edge of the larger lesion. The rest is merely barium.

CASE 33172

PRESENTATION OF CASE

A fifty-one-year-old housewife entered the hospital because of jaundice.

Three and a half months before admission the patient had noted the onset of anorexia and epigastric distention. Six weeks before entry generalized pruritus began. On two occasions the temperature was elevated to 99.2 and 99.4°F. Dark urine was noted a month before entry, and a week later definite jaundice appeared. With the onset of the jaundice the stools became light yellow. The patient believed that she had lost 10 to 15 pounds in the six months preceding admission. No unusual intolerance to fatty food had developed, but she had always avoided them because she thought that they caused hyperacidity. She denied using alcohol or drugs. Two months before admission and again a month later, she had visited a sister who was hospitalized with infectious hepatitis.

Except for a single attack of rheumatic fever in childhood, the past history was noncontributory.

On examination the patient was thin and fretful. The skin and scleras were yellow. Over the bridge of the nose there were several telangiectases. The lungs were normal. An early Grade II diastolic murmur was heard at the apex. The liver edge, which was palpated 4 cm. below the ribs in the anterior axillary line and 8 cm. below the xiphoid, was smooth, firm and nontender. The tip of the spleen was palpable on deep inspiration. The uterus was firm, rounded and about the size of an orange.

The temperature was 98°F., the pulse 89, and the respirations 19. The blood pressure was 140 systolic, 80 diastolic.

Examination of the blood revealed a hemoglobin of 13.2 gm. per 100 cc. and a white-cell count of 11,000, with 72 per cent neutrophils. The urine was cloudy and orange. The specific gravity was 1.020; there was no albumin, sugar or bile, but urobilinogen was present in a dilution of 1:80; there were 6 epithelial cells per high-power field in the sediment. The stools were tan to light grayish tan. A guaiac test was + on two occasions, and negative on one. The total protein was 6.9 gm. per 100 cc., with an albumin-globulin ratio of 1.4, and the cholesterol was 208 mg., the nonprotein nitrogen 21 mg., the vitamin A 70 mg., the carotenoid 40 mg., and the alkaline phosphatase 7.7 Bodansky units per 100 cc. The serum bilirubin was 4.2 mg. per 100 cc. direct and 5.6 mg. indirect. The cephalin-flocculation test was negative after twenty-four hours and + after forty-eight hours. The prothrombin time was 13 seconds (control, 15 seconds). A plain film of the abdomen was normal. There was no filling of the gall bladder during the Graham test.

In the hospital the patient continued to have slight itching, moderate jaundice and a normal temperature. On the third day the serum turbidity test* was 4.3 units at the end of thirty minutes, and the thymol flocculation test was ++++ at forty-eight hours.

On the thirteenth day the phosphatase was 11.3 Bodansky units per 100 cc., the phosphorus 3.5 mg., the bilirubin 5.8 mg. direct and 7.5 mg. indirect. The prothrombin time was 19 seconds (control, 16 seconds). Five milligrams of bromsulfalein per kilogram of body weight injected intravenously showed 30 per cent retention of the dye in forty-five minutes.

The liver remained about the same size. Subsequently the jaundice increased slightly, and the stools became definitely clay colored and were only slightly positive for bile. On the twenty-fifth hospital day, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ALLEN G. BRAILEY: This case illustrates a frequent and often puzzling problem — the cause of jaundice. Jaundice is the visible expression of hyperbilirubinemia, which in turn may be caused by increased blood destruction or by inability of the damaged liver to excrete the bile adequately. The first possibility — namely, that this patient had hemolytic jaundice — seems out of the question. In its favor are the absence of bile in the urine and some evidence of enlargement of the spleen, but the course of the disease was not that of acholuric jaundice. No familial history of this condition was obtained, and tests for spherocytosis and increased fragility of red cells were not done. Obviously, the service did not consider hemolytic jaundice, and I think that we should not do so either.

It is much less easy to dispose of the suggestion that the patient had some form of intrahepatic parenchymal disease. For example, the entire course

*Neefe, J. R. Results of hepatic test in chronic hepatitis without jaundice: correlation with clinical course and liver biopsy findings. *Gastroenterology* 7:1-19, 1946.

is not inconsistent with infectious hepatitis. The onset was rather protracted, but such an onset certainly occurs. It is thrown in for good measure that her sister had been hospitalized with infectious hepatitis. This patient's illness, however, appears to have antedated exposure to her sister's infection. She had had jaundice for a total of at least six weeks, but that is not an unusual duration, nor is it unusual for the jaundice to be getting worse instead of better at the end of such an interval. It is reported that at the end of six weeks the stools became definitely clay colored, and this ought to mean, if she had hepatitis alone, that the liver cells were so severely damaged that they were no longer secreting bile. Opposed to such a notion is the rather remarkable lack of evidence of parenchymal damage. We are presented with an impressive array of liver-function tests but for the most part they were all within normal range — the total protein, the albumin-globulin ratio, the cholesterol, the cephalin flocculation, the vitamin A and the prothrombin time. The thymol-turbidity test gave a borderline result and points, but only uncertainly, to liver-cell disease. Since I believe that there is too little evidence of liver-cell disease as the primary trouble, I rather reluctantly relegate hepatitis of any sort to second place.

A better possibility seems to be that the jaundice was due to biliary obstruction. This would adequately account for all the laboratory data presented. In fact, the ratio of direct to indirect serum bilirubin is some slight evidence for jaundice on an obstructive basis. But was the obstruction due to stone within the lumen of the duct or to pressure, presumably from cancer, without? I am sure that there is no way in which we can resolve this question with any certainty. Without doubt, a stone is a real possibility, and it is easy to make the mistake of attaching too much importance to the slender clues that the record contains in favor of cancer. For instance, the fact that the patient had no pain is statistically slightly in favor of cancer. The tip of the spleen was felt. This may occur with either type of obstruction, but again it is a little more frequent with cancer. The clinical course was quite steadily progressive over a total of nearly five months — a picture at least consistent with cancer. Dr. David Riesman used to consider preicteric itching suggestive evidence of malignant obstruction. The liver edge appeared to be abnormally low. One cannot make much of that. It may have been merely ptotic, but if it was really enlarged, it appears not to have enlarged rapidly, for it was said not to have been tender.

Since I must make a diagnosis I shall vote for biliary obstruction due to cancer — the cancer being primary in the pancreas, the ampulla, the gall bladder or even the liver itself. The cancer may have been metastatic, provided the metastasis happened to develop at the porta hepatis. In addition, the patient probably had rheumatic heart disease and enlargement of the uterus due to fibroids.

It is stated that on the twenty-fifth day an operation was performed. The possibilities of a benign and remediable condition are excellent, and the patient's condition certainly indicated a liver biopsy and probably an exploratory laparotomy.

DR. CLAUDE E. WELCH: Since Dr. Brailey made a diagnosis of cancer, I should like to ask him if he could be more specific. If the surgeon is going to explore, it makes a difference whether the lesion is primary or metastatic. From the history, I think that one can be more specific.

DR. BRAILEY: On a statistical basis, cancer of the head of the pancreas is the most probable, but I should be glad to have you tell me.

DR. WELCH: The gall bladder was not palpable, which is distinct evidence against cancer of the head of the pancreas.

DR. BRAILEY: The patient was a fairly thin person, and the gall bladder might have been expected to be palpable. I do not attach significance to the Graham test. Do you think that nonvisualization is in favor of carcinoma of the gall bladder?

DR. WELCH: No; I do not believe so, because she was deeply jaundiced. No mass was palpable that could be distinctly felt as carcinoma of the gall bladder. She could have had carcinoma of the duct, but that is all she could have had of that nature.

DR. DANIEL S. ELLIS: At the time the Graham test was done, the patient was barely jaundiced. The jaundice seemed to be fading.

DR. BRAILEY: That gives a slightly different picture. I had the impression that she had a fairly steady course.

DR. ELLIS: That is the reason the Graham test was done at the time. Clinically there was enough change to indicate that she seemed to be getting better, and we thought that we might get more evidence from it.

DR. TRACY B. MALLORY: An attempt was made to get additional information on this patient by liver biopsy, which I believe was rather more confusing than helpful. Dr. Ellis, will you take up the story?

DR. ELLIS: This case was one that makes liver disease so fascinating to work with. When the patient was first seen in the office about two weeks before admission to the hospital, the history seemed to be more consistent with a diagnosis of cancer than anything else. One was struck by how well she looked. The stools when first seen were light tan, and she had bile in the urine. I elected to follow her for two weeks at home; the stools became dark, and the degree of jaundice stayed about the same. The itching for practical purposes ceased. At the end of that period, it was believed that there had been no real improvement and that the diagnosis was still not proved. Accordingly, she was admitted to the hospital for aspiration liver biopsy. The tests

referred to above were done on admission, and on the fourth day a biopsy was performed. On the basis of this biopsy report, which Dr. Mallory will describe, we thought that she had intrahepatic disease. The palpable spleen lent more evidence to this diagnosis, and there was no question that the spleen was large enough to be palpable. Largely on the basis of the biopsy report, we elected to give medical treatment for two more weeks.

DR. MALLORY: The aspiration biopsy showed an unusual appearance on which I could not make a diagnosis. The liver cells were obviously abnormal. A portion of them were fat containing, and some were markedly vacuolated but showed a hydropic type of vacuolization rather than that due to fat. That is an unusual finding in biopsy material, and I do not know how to interpret it. There was scanty inflammatory infiltration in the portal areas. I was unable to make a diagnosis of infectious hepatitis, but I did think that there was intrinsic liver disease of some unknown character. That was as far as we were able to go at that time.

DR. ELLIS: On that basis we gave intensive medical therapy, but at the end of two weeks three factors were obvious: the patient was no better, the jaundice was marked, and the stools were clay colored, lighter than before. So far as the laboratory evidence was concerned, she had a rising phosphatase, which bothered us considerably. She started with a low phosphatase but before operation it was up around 15 units. Since she had had the best treatment that we could give her and was getting worse, we decided to perform an exploratory laparotomy. Preoperatively all of us believed that she had intrahepatic disease, the basis of which we hoped would be some obstructive phenomenon that had given rise to an ascending infection and a biliary cirrhosis or ascending cholangitis, although there was a good probability that we would find cancer somewhere.

DR. MALLORY: Dr. McKittrick, can you tell us something about the operation?

DR. JOHN B. MCKITTRICK: I was not present at the operation, which Dr. Leland McKittrick performed. The findings were somewhat unusual in one respect — the patient had a completely collapsed external biliary tree. The gall bladder was just as though one had aspirated it and erupted it of all bile. The common duct was so small that it was almost impossible to get a needle into it. Two or three masses were palpable on the dome of the liver, which to Dr. McKittrick did not feel like metastases. The liver itself was somewhat reddish. The spleen was enlarged. There was some white scarring that was palpable throughout the liver. In the left half of the pancreas, there was a definitely palpable tumor. The liver was biopsied, as was the tumor in the pancreas.

CLINICAL DIAGNOSIS

Carcinoma of pancreas?
Intrahepatic disease?

DR. BRAILEY'S DIAGNOSES

Biliary obstruction, due to carcinoma.
Rheumatic heart disease.

ANATOMICAL DIAGNOSES

Adenocarcinoma of pancreas, with liver metastases.
Biliary cirrhosis of liver, slight.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Biopsy of the liver showed that, in the interval between biopsy and operation, the vacuolization of the liver cells, both fatty and hydropic, had entirely disappeared, presumably as the result of the dietary treatment that Dr. Ellis had carried out. In one respect, however, namely, bile stasis, there was no improvement; in fact this was considerably intensified. Bile staining of the Kupffer cells was particularly prominent. The portal areas had become wider, and in many of them we found strands and small clumps of frankly neoplastic cells. Biopsy of the pancreas showed an adenocarcinoma, which was undoubtedly the primary site of the neoplastic disease.

I do not believe that I can explain the collapse of the extrahepatic bile ducts with any certainty. The widespread tumor infiltration of the portal areas within the liver may have produced obstruction of the small intrahepatic bile ducts.

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DIAGNOSIS OF AMEBIASIS BY STOOL EXAMINATION

During the past year the results of several studies on dysentery and diarrhea in members of the armed forces returning from tropical areas have been published.[1, 2] These indicate to some extent the number of persons who had these diseases while overseas. The majority of these men are no longer in the service, and a certain percentage are being seen by clinicians because of unexplained persistent diarrhea, diarrhea alternating with constipation or vague abdominal symptoms.

Since a variety of causes can be responsible for these intestinal conditions and since the clinical symptoms are frequently nonspecific, it is necessary to find an organic basis or a pathogen responsible for the condition, with subsequent elimination of the latter if discovered. Although clinicians can explore the physiologic bases for these symptoms by routine procedures and although reliable stool cultures for pathogenic bacteria are readily obtained, there is a scarcity of laboratory technicians skilled for the diagnosis of infections due to intestinal parasites.

The majority of human helminthic infections have a definite geographic distribution. For example, a person who has never been outside New England could not have filariasis or hookworm infection, but a man with a period of wartime service on certain Pacific islands might have become infected with both these helminths. Thus, knowledge about the patient's travels and the conditions under which he lived in endemic areas is helpful in arriving at the possibility of infection and the specific helminthic infection suspected. Unfortunately, infection with *Endamoeba histolytica*, the causative agent of amebic dysentery, is universal, although it is more prevalent in the tropics than in the temperate zones. Consequently, infection with this organism can take place anywhere, if food or water contaminated with the infective cysts is ingested.

In examining a stool for parasites, the technician must be able to recognize not only various stages of the pathogen but also nonpathogenic organism tissue cells, macrophages and debris. A reliable diagnosis is not readily obtainable because the majority of laboratory technicians are not properly trained or lack the necessary equipment. It is a rare technician who can make a satisfactory diagnosis by following a textbook or laboratory manual. Morphology of the organisms, staining technics and cultural procedures must be learned and mastered. Indeed, practical experience gained during a period of intensive training is usually necessary if the technician's results are to be reliable. In addition, the clinician, intern or nurse should know that fecal samples for examination should be free of antiseptics and urine and should be delivered to the laboratory within an hour. If the stool cannot be examined immediately, it should be placed in the refrigerator, not in the incubator. Furthermore, normally passed stools are preferable if the laboratory technician is not highly skilled: purged stools

give a higher percentage of positive results, but the presence of tissue cells and macrophages may confuse the novice.

Textbooks of clinical pathology, parasitology and tropical medicine give the usual procedures for the recognition of amebas in stools. These include a record of the gross appearance of the specimen, including the presence or absence of mucus, pus or blood. Microscopical examination of a fresh preparation consists of a search for active stages of the protozoa or their cysts, as well as tissue cells, erythrocytes and *Blastocystis hominis* (a nonpathogenic, yeast-like organism). If cysts are present, a presumptive diagnosis can often be made by the examination of an iodine-stained preparation, but films stained by the iron-hematoxylin method are usually required to make a specific diagnosis. Cultivation of the specimen for *E. histolytica* is a useful supplementary procedure, but it is not considered practical for routine laboratory purposes unless the technician has had experience with this technic. Concentration methods, using a saturated solution of sodium chloride or zinc sulfate flotation, are satisfactory for the detection of nonoperculated helminthic eggs and of low concentrations of cystic amebas. It must be remembered, however, that such methods are useful only to detect the cystic stages, *not* the active stages, which are present in patients with acute amebic dysentery and in a certain percentage of carriers. The complement-fixation test has been improved and is sometimes used to detect the presence of infection with *E. histolytica*, having proved particularly valuable in suspected cases of hepatic amebic infection. It requires skill, and only a few laboratories are equipped to make the test.

Interpretation of negative or positive findings should depend on the clinical symptoms of the patient. Amebas are not passed at a constant rate in the feces, so that a negative finding in one or several specimens does not necessarily mean that the patient is not infected, nor should it invalidate the results of other laboratory examinations. If suspicion of infection with *E. histolytica* persists, additional stool specimens should be examined. Proctoscopic or sigmoidoscopic examination is helpful in recognizing ulceration in the lower bowel. If ulceration is present, scrapings from the crater of the ulcer should be examined, since this is the likeliest place for the presence of *E. histolytica*. Furthermore, a positive diagnosis for *E. histolytica* in the absence of symptoms indicates that the patient is a carrier, and the organism should be eliminated by a course with an amebicidal drug, because of the danger of transfer of amebas to others.

The above statements have been made not with the view to create alarm regarding the incidence of amebiasis but to point out the need for improved training of hospital laboratory technicians in the performance of stool examinations for the presence of amebas, to discuss briefly the conditions required for a reliable diagnosis and to point out the meaning of positive and negative findings.

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THE QUALITY OF MERCY

The ancient Israelites, who first conceived the idea of one god for all people, were also the first to credit that Being with absolute justice, stern as it might be, and later with the quality of mercy. Mercy, so far as we know, had been a scarce commodity in the world up to that period. Sapient man had been in existence for three or four hundred centuries, but he had lived by the law of a tooth for a tooth and an eye for an eye, and precious little mercy had entered into it.

Mercy, which Webster considers to be "forbearance from inflicting harm . . . ; compassionate treatment, especially of the suffering or helpless," is an emotional attribute that might be considered almost spiritual. Rarely, if ever, can it be conceded to lower forms of life, yet few men can be believed to be utterly without it.

Animals show only rudimentary social emotions. They care for their young or destroy them; the dog risks his life for his master or languishes on his grave; they hunt in packs. Certain insects lead highly organized community existences and lend mutual aid, as do bees and ants and wasps, but except occasionally for the dog to his master or perhaps mated pairs to each other, animals do not know the emotion of compassion. That has been reserved for man.

Shakespeare has given us our greatest dissertation on mercy, which, as we all know, "blesseth him that gives and him that takes." The scepter of a king, we are told, shows the might of temporal power.

> But mercy is above this temporal sway,
> It is enthroned in the hearts of kings,
> It is an attribute to God himself;
> And earthly power doth then show likest God's,
> When mercy seasons justice.

We had believed, until a few short years ago, that man might be on an upward path, that his moral insight might be keeping pace with his intellectual achievements, but we have learned since then that ethical conduct depends on certain little understood and unreliable factors. Too often in man's history it has happened that just as he reached a point in progress where he thought that he might pause and pose for the photographers, at that point the shooting began. Man can apparently become without compassion.

So the inhabitants of the world find themselves again resuming the search for the causes of man's inhumanity to man. Those who are aware of the need are doing it as individuals, as groups, as nations and as organizations of nations. Among the leaders in the search must be the men and the professions among men that, knowing most about suffering, have chosen to be greatest in compassion.

The profession of medicine, freed to a large extent from mystery and magic, has shown itself for centuries to be the calling of the Samaritan. It has combed the battlefield unarmed, seeking only to lighten suffering where it might be found. Its followers are in a position where, by themselves and through their organized fellowships, they must expect to share leadership, to set examples and to stir consciences in still another attempt to shape man's destiny according to a pattern of universal tolerance and mercy.

OBITUARY

CHARLES FAIRBANKS PAINTER

1869–1947

Dr. Charles F. Painter died suddenly at his home on January 6, 1947. He was a direct descendant of an old Virginia family, although he was born in Grand Haven, Michigan, on May 19, 1869.

On graduating with a degree of A.B. in one of the earliest classes of the newly founded Johns Hopkins University in 1891, he came to Boston and studied medicine at the Harvard Medical School, receiving the degree of M.D. in 1895. He was a member of the first four-year class at Harvard Medical School, where he was associated with such well known classmates as Joseph A. Capps, Arthur L. Chute, E. Amory Codman, Harvey Cushing, Elliott P. Joslin, Timothy Leary, William H. Robey and Franklin W. White. Harvey Cushing was closely associated with Charles Painter during his four years at the medical school, and it was Cushing who wrote in a letter to his father dated January 31, 1892: "Painter, I like very much. He is slow, but hangs on to everything he gets. He hails from Great Barrington and is a great big solid whole-souled creature such as one likes to meet."

He served his internship at the Massachusetts General Hospital and later served at the old Children's Hospital, where he was associated with E. H. Bradford, Robert Lovett and other brilliant orthopedic pioneers of the time. He himself became an outstanding orthopedic surgeon and engaged in active practice of this specialty. For many years he was surgeon-in-chief at the Carney Hospital.

Between 1913 and 1922 he was dean of Tufts College Medical School. This was the decade of World War I, with all the turmoil created by that conflict in the field of medical education, and this service indicates Dr. Painter's administrative capacity. He also had strong literary interests and was always ready to serve on committees or otherwise when these interests could be brought to bear on current problems. While dean at Tufts Medical School he created a Chair of the History of Medicine and occupied it himself for a number of years. He edited the *Yearbook of Orthopedic Surgery* and served for a long time on the editorial board and briefly as editor of the *Journal of Bone and Joint Surgery*. He was president of the American Orthopaedic Association in 1915 and 1916.

In 1929 Dr. Painter was chosen librarian of the Boston Medical Library, in which position he served until 1937. He continued the high standards of the Library although it was his lot to hold this position during a period of decreasing financial support. That he was able to prevent any material reduction of service to the Library members and the public under these circumstances indicates his devotion to the things that the Library stands for and to the Library itself.

Dr. Painter's death closes the life of a man who was a scholar as well as a physician and surgeon and who became one of the foremost orthopedic surgeons of his day. He was a devoted student of medical history and literature, and one may well understand Cushing's comment that he was "a solid whole-souled creature such as one likes to meet."

H. R. V.

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council will be held in the Georgian Room of the Hotel Statler, Boston, on Monday, May 19, 1947, at 7:00 p.m. This meeting will be preceded by the Cotting supper, which will be served in Parlors A and B of the same hotel at 6:00 p.m.

Business:

1. Presentation of record of the stated meeting of the Council held February 5, 1947, as published in the *New England Journal of Medicine*, issue of April 17, 1947.
2. Reports of standing and special committees.
3. Election of officers and orator.
4. Appointment of committees for ensuing year.
5. Such other business as may lawfully come before the meeting.

MICHAEL A. TIGHE, *Secretary*

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

GREELEY — Philip H. Greeley, M.D., of Dover, died December 20, 1946. He was in his seventy-seventh year.

Dr. Greeley received his degree from Dartmouth Medical School in 1897. He was a fellow of the American Medical Association.

His widow and two sons survive.

SPRAGUE — Fred A. Sprague, M.D., of Concord, died December 3, 1946. He was in his seventy-fourth year.

Dr. Sprague received his degree from Baltimore Medical College in 1906. He was a veteran of both the Spanish American War and World War I. He was a fellow of the American Medical Association.

His widow, two sisters and a brother survive.

MISCELLANY

A BORDEN AWARD TO DR. GAMBLE

The Borden Awards, which were established in 1936 by the Borden Company Foundation, Incorporated, to recognize and encourage outstanding research achievements in the United States and Canada, are administered by eight professional and scientific associations, each of which annually selects someone to receive the award who has reported notable research in his particular field.

To the American Academy of Pediatrics is delegated the responsibility of selecting an investigator who has performed outstanding research in the nutrition of infants and children, and for the year 1946 it chose Dr. James L. Gamble, professor of pediatrics at Harvard Medical School and visiting physician at the Children's Hospital, Boston. The citation reads: "For pioneer work over a period of many years in the field of salt and water balances in the human body, with particular reference to infants and children."

CORRESPONDENCE

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held March 21, it was voted to suspend the registration to practice medicine of Dr. Frederick T. Butler, formerly of 166 Townsend Street, Roxbury. Dr. Butler was cited for a hearing under General Laws, Chapter 112, Section 61, but was unable to appear because he is a patient at the Boston State Hospital.

At the same meeting, the Board also voted to revoke the registration to practice medicine of Dr. David Ginsburg, 1938 Main Street, Springfield, following his conviction in court of having performed an abortion.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

DDT "POISONING"

To the Editor: The report of a case of periarteritis nodosa, by Drs. William R. Hill and C. Robert Damiani, which appeared in the December 19, 1946, issue of the *Journal*, was read with considerable interest. It was an able and convincing presentation of a case of that rare and little understood disease. If it had been presented as such, it would have been much less sensational, but at the same time would have been a positive rather than a negative contribution to medical knowledge.

The title and conclusions add one more item to the list of source material that has deluded these authors and will delude still others into erroneous diagnoses of DDT poisoning. Such an erroneous diagnosis in itself may well be the cause of fatalities, for example, the man in New Jersey who developed a constricting pain in the chest while spraying DDT. His doctor, believing that DDT was highly poisonous, advised the victim to run up and down out of doors and breathe deeply in the fresh air. The man followed this advice and proceeded to die, but in the face of a history of a preceding coronary heart attack, the preliminary newspaper reports of a DDT fatality were corrected and did not become a part of medical literature.

The circumstances surrounding the exposure to DDT in the present case deserve careful consideration.

(1) The total amount sprayed in the workroom was 130 cc. of 6 per cent DDT, and presumably the largest portion of this was sprayed hours before the man came to work. No hand sprayer is made which will keep more than a fraction of 1 per cent of the atomized DDT from settling on the walls or floor, either at the moment of spraying or within a few minutes thereafter.

(2) Even with aerosol atomizers, a very large portion settles out quickly and the remainder could not by any stretch of the imagination have concentrated itself in the lungs or on the skin of the victim in a quantity of the magnitude of 1 per cent of the total which he himself sprayed.

(3) This should be recognized as an infinitesimal dose, even from the most carelessly studied cases of DDT poisoning cited. Reference to the works of Neal et al. should be given considerably more weight than the others cited because of a vastly greater background of toxicologic experience, and because Neal's studies are particularly thorough and scientific investigations of DDT toxicology.

The low toxicity of DDT is attested by a wide experience with its use. I have seen men spraying scores of gallons of DDT a day indoors, day after day, and know of men who have done this for upward of a year. I have seen mixing by hand of thousands of gallons of oily solutions of DDT day after day with frequent wetting of arms and hands, with no ill effect.

The supposition that this patient had become sensitized is not supported in any way, not even by history of prior exposure. Tremors are a sign of acute toxicity, develop early and disappear with recovery. In the case cited, tremors did not develop until a month after an insignificant exposure, and a few days before death in a disease affecting the blood vessels of the brain. The offering of tremors as evidence of the validity of the DDT assumption in this case is an indication of faulty logic as well as a misunderstanding of the true toxicity of DDT. This misunderstanding should not be propagated.

This comment is properly divided into two parts. No slightest exception is taken to the clinical, laboratory and pathological description of a death due to periarteritis nodosa. But the title, "Death following Exposure to DDT" is considered misleading and false in its implication. The reasoning is based on false and inadequate premises of exposure and known toxicity of DDT. The assumption, repeated in the conclusion, that DDT was the probable cause of the fatal disease in this case and the statement "It is reasonable . . . to assume that DDT . . . possesses . . . allergenic properties and should be included among the drugs capable of producing a sensitizing reaction . . . " are entirely unjustified.

Of all possible explanations of the present case, this one is the most highly imaginative and quite likely to cause harm and confusion in the medical literature.

R. W. Babione
Captain (MC), U.S.N.

413 Tyler Place
Alexandria, Virginia

* * *

Captain Babione's letter was referred to Dr. Hill, whose reply is as follows:

To the Editor: Perhaps the title of this paper is somewhat misleading since death could not be primarily attributed to DDT. Nonetheless, the clinical picture was quite consistent with a sensitization reaction, and the fact that this became manifest less than twenty-four hours after exposure to DDT makes the latter the presumptive exciting agent. The finding of the lesions of periarteritis in the biopsies of the skin and muscle is further evidence of an allergic reaction. It is well known that sensitization may result from infinitesimal amounts of allergenic agents.

William R. Hill, M.D.

520 Commonwealth Avenue
Boston

BOOK REVIEWS

Diseases of the Skin. By George C. Andrews, M.D. Third edition. 8°, cloth, 937 pp., with 971 illustrations. Philadelphia and London: W. B. Saunders Company, 1946. $10.00.

Dr. Andrews has thoroughly revised this new edition of his standard textbook on dermatology. Almost every paragraph has been revised by the deletion of obsolete material and the addition of recent discoveries. Treatment with the sulfonamides, penicillin, streptomycin and other antibiotics has been incorporated throughout the text. Discussions of more than sixty new skin diseases have been added. New chapters have been inserted with the intention of aiding those who desire to take the examinations of the American Board of Dermatology and Syphilology. All prescriptions have been rewritten in the metric system and in Latin so far as practicable. Many new illustrations have been added. The *Standard Classified Nomenclature of Disease*, compiled by the National Conference, has been followed, with minor exceptions. Every effort has been made to keep the classification simple, easy to use and practical. The text is well written and well organized. Special prominence is given to the more frequent dermatoses. A selective bibliography is appended to each chapter. The text is well printed with a good type on good paper, and the illustrations are adequate. This book should be in all medical libraries and should prove useful to all physicians interested in diseases of the skin.

Electrocardiography in Practice. By Ashton Graybiel, M.D., and Paul D. White, M.D. With the assistance of Louise Wheeler, A.M., and Conger Williams, M.D. Second edition. 8°, cloth, 458 pp., with 323 illustrations. Philadelphia: W. B. Saunders Company, 1946. $7.00.

This new edition has been revised in the light of recent advances in the subject. A new section on precordial leads has been added in the first part, and illustrations of normal and abnormal multiple precordial electrocardiograms have been introduced throughout the text. The fifth part contains a new series of test electrocardiograms presented in random fashion, for practice in interpretation. Two new topics, unipolar and esophageal leads and the effects of exercise and low oxygen tests, have been added in appendixes. Four new tables are of special interest: the first shows the effects of the so-called "indifferent electrode"; the second tabulates the disorders of rhythm; the third shows the characteristic changes in the electrocardiogram in various diseases affecting the heart; and the fourth lists the changes resulting from the administration of various drugs and the effect of various physiologic influences. The usefulness of multiple chest leads is fully discussed.

This standard monograph should be in all medical libraries and should prove of value to all physicians interested in diseases of the heart.

Electrocardiography, including an Atlas of Electrocardiograms. By Louis N. Katz, M.D. Second edition, thoroughly revised. 4°, cloth, 882 pp., with 525 illustrations. Philadelphia: Lea and Febiger, 1946. $12.00.

The author has thoroughly revised this standard work, bringing up to date the subject matter and the bibliography and rewriting large portions of the text. The additional material has increased the size of the volume about 50 per cent, necessitating the division of the text into twenty-three chapters instead of the sixteen in the previous edition. The illustrations have also been completely revised, one hundred and twenty-five having been deleted and two hundred and forty-nine added. Summary tables and new charts showing the salient features of normal and abnormal deflections, of specific patterns and of various arrhythmias have been introduced to make the volume more suitable for beginners. A third chest lead — Lead CF$_5$ — is described, and its use under various circumstances considered and illustrated, because the author is convinced from his experience in over 5000 cases that this chest lead contributes greatly to the evaluation of abnormalities of the heart, especially of heart strain, intraventricular block and coronary disease.

The report of the special committee of the American Heart Association on the establishment of a universal nomenclature for the several deflections of the electrocardiogram is included, and its recommendations are largely followed with a few exceptions. A new chapter on terminology has been introduced. A section on the principles involved in the electrical manifestations of the heart has been added, and recent concepts of the theory of the electrocardiogram and findings on the properties of the heart have been included in the revision. War experience having shown that the variation in normal electrocardiograms was greater than supposed, the standards of normality have been completely revised and the effect of posture, body build and the physiologic state of the subject have been discussed in a separate section. The chapters on transient electrocardiographic changes in acute and chronic illness and in patients under the influence of drugs have been expanded to include recent information. The conditions giving rise to electrocardiograms simulating the coronary pattern are emphasized in a separate chapter, and coronary pain and coronary circulation have been included to make the subject of coronary disease more complete. The material on the management of cardiac arrythmias and coronary disease has been expanded for the benefit of the clinician. A new chapter on interference and dissociation has been added, as well as material on several unusual and complex arrythmias and new information on the nature of intraventricular block and the combination of the shortened PR interval and the prolonged QRS complex.

Despite these major additions and expansions the scope and purpose of the work have not been altered. A selective bibliography is appended to each of the three sections of the text. The book is well printed with a good large type, and the large number of tracings are uniformly clear and distinct. This treatise should be in all reference medical collections.

Nursing in Commerce and Industry. By Bethel J. McGrath, R.N., for the National Organization for Public Health Nursing. 8°, cloth, 356 pp. New York: The Commonwealth Fund, 1946. $3.00.

This volume provides a much needed authoritative up-to-date text in industrial nursing. Mrs. McGrath is well qualified for the task of writing such a text, since she was formerly industrial nursing consultant to the National Organization for Public Health Nursing and is chief industrial nursing consultant to the American Association of Industrial Nurses and industrial nurse of the Powers Dry Goods Company, Minneapolis. The book has been planned for the nurse already practicing in the field.

Dr. Alice Hamilton, well known authority on industrial poisons, has written an interesting and informative introduction in which she points out the great advances in industrial medicine and nursing that have taken place during the last thirty years. The material is well organized, and the text well written and documented.

The author defines industrial nursing as the application of nursing skill to groups of men and women at their places of work for the purpose of helping them build and maintain their best health, and the rendering of prompt and efficient nursing assistance when they become ill or injured.

The preliminary chapters are devoted to the history of industrial nursing in the United States, industrial organization, the nurse, the nurse's duties and responsibilities and physical facilities for the nursing service, as well as an important chapter on relations with employees and employee organizations.

Then in order follow discussions of the health of the worker, occupational accidents and hazards, disease hazards, non-occupational illness and accidents, mental hygiene, including malingering, sight conservation (written by Eleanor Mumford), orthopedic nursing (written by Katherine Ott), nutrition, problems peculiar to women in industry and the control of communicable diseases. The concluding chapters concerning records and reports were written by Heide L. Henriksen, and those on rehabilitation, workmen's compensation, industrial welfare activities and hourly nursing service by an outside agency by Lucille M. Harmon.

An appendix contains important miscellaneous material, including equipment for the health service, a concise manual for emergency procedure, a formula for an industrial cleanser, standards for maternity care and employment of expectant mothers, and equipment and technic for eye examinations.

The book is well printed with a good type on good soft paper and is not too heavy for the size of the volume. It has an adequate index. It should be in all medical, public-health and public libraries, as well as in all industrial and commercial libraries.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Cornell Conferences on Therapy. Volume 1. Edited by Harry Gold, M.D., managing editor, David P. Barr, M.D., Eugene F. DuBois, M.D., McKeen Cattell, M.D., and Charles H. Wheeler, M.D. 8°, cloth, 322 pp. New York: The Macmillan Company, 1946. $3.25.

The topics reported in these informal conferences, first held in 1937, cover the whole field of therapeutics and are a selection from a large number. The following subjects are discussed: the doctor's bag, use and abuse of bed rest, heart failure, digitalis *vs.* digitoxin, mercurial diuretics, subacute bacterial endocarditis, abdominal distention, intestinal infections, diseases of the eye, poisoning and the Rh factor.

A Textbook of Gynecology. By Arthur H. Curtis, M.D., professor and chairman of the Department of Obstetrics and Gynecology, Northwestern University Medical School, and chief, Gynecological Service, Passavant Memorial Hospital, Chicago. Fifth edition. 8°, cloth, 755 pp., with 455 illustrations, chiefly by Tom Jones. Philadelphia: W. B. Saunders Company, 1946. $8.00.

This standard treatise has been extensively revised in all but a few chapters. The section on ovarian tumors has been expanded, and in the chapter on other tumors of the uterus, two new topics, sarcomatoid growth of the endometrial stroma and hypertrophy of the uterus, have been added. The endocrinographic disturbances have been co-ordinated into a separate division providing a consideration of the subject in its entirety. Penicillin therapy has been added to the topic of gonorrheal infection. A large number of new photographs and photomicrographs have been added to the text. The book is well printed with a good type on good paper. The illustrations are excellent. It is recommended for all medical libraries as a reference book.

English-French and French-English Technical Dictionary: Metallurgy, mining, electricity, chemistry, mechanics, sciences. By Frances Cusset. 16°, cloth, 590 pp. Brooklyn, N. Y.: Chemical Publishing Company, Incorporated, 1946. $5.00.

This small dictionary with terms in two parts, French-English and English-French, is well organized and printed with contrasting type on good paper. The text is not limited to single words but has a large number of short word combinations. It is recommended for all library reference collections.

Proceedings: Conference on diagnosis in sterility. Sponsored by the National Committee on Maternal Health, January 26-27, 1945, New York City. Edited by Earl T. Engle, Ph.D. 8°, cloth, 237 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1946. $5.00.

The papers contained in this volume of proceedings cover the various aspects of human sterility. Among the topics discussed are semen examination, testicular biopsy, the role of the accessory glands, chronic hemospermia and its treatment with estrogen, endometrial biopsy, basal body-temperature curves, examination of cervical mucus, tubal-patency tests, history taking of infertile couples and a working hypothesis of the mechanism of sterility. The book is well published, and is recommended for all medical libraries and for gynecologists and physicians interested in the subject.

Physiotherapy. By Thomas F. Hennessey, M.D., dean and director, Massachusetts School of Physiotherapy, Boston. 8°, paper, 23 pp. Boston: Bellman Publishing Company, Incorporated. 75 cents.

This outline is one of a series of seventy-five occupational booklets used in connection with guidance work. It discusses physiotherapy as a special field in its educational and vocational aspects.

Irish Medical Directory and Hospital Year Book — 1945. Eighth edition. 8°, cloth, 296 pp., illustrated. Dublin: The Parkside Press, Limited, 1946. 10 shillings, 6 pence.

This reference work is divided into three parts. The first is clinical and contains a number of special articles on delivery, abortion, cancer of the cervix, tuberculosis in infancy, rickets, diarrhea and social service in hospitals. The second comprises an alphabetical list of all physicians in active practice in Ireland, with their qualifications, hospital connections and important medical writings. The third is a list of hospitals in Ireland arranged by county and giving information concerning the administration, number of beds and nurses and public or private status.

Protozoology. By Richard R. Kudo, D.Sc., professor of zoology, University of Illinois. Third edition. 8°, cloth, 778 pp., with 336 illustrations. Springfield, Illinois: Charles C Thomas, 1946. $8.00.

This standard textbook, first published in 1931, has been thoroughly revised and brought up to date. The chapters on physiology, reproduction, and variation and heredity have been largely rewritten and enlarged. New material has been added on major groups and phylogeny, and on collection, cultivation and observation. Sixty-nine new figures have been added, and a detailed comprehensive index ends the volume. Short bibliographies are appended to each chapter. The book is recommended as an authoritative reference work.

Diabetic Care in Pictures: Simplified statements with illustrations prepared for the use of the patient. By Helen Rosenthal, B.S., associate dietitian in the Food Clinic, Boston Dispensary, and assistant in medicine, Tufts College Medical School; Frances Stern, M.A. (honorary), chief of the Food Clinic, Boston Dispensary, instructor of medicine, Tufts College Medical and Dental schools, special instructor in dietetics in social service, School of Social Work, Simmons College, and associate in nutrition, School of Home Economics, Simmons College; and Joseph Rosenthal, M.D., chief, Diabetic Clinic, assistant medical director and medical supervisor, Domiciliary Medical Service, Boston Dispensary, assistant professor of medicine, Tufts College Medical School, and associate physician, Joseph H. Pratt Diagnostic Hospital. 8°, cloth, 150 pp., with 137 illustrations. Philadelphia: J. B. Lippincott Company, 1946. $2.00.

This manual is written in simple language and is adequately illustrated with photographs, charts and drawings. It is designed for the use of the diabetic patient. The subjects covered include diet, insulin and its reaction, acidosis and

coma, blood and urine tests, skin injuries, and personal and special hygiene, especially of the hands and feet. A short chapter on personal and social factors concludes the text. The ring type of binding employed is not suitable for hard usage in the home. This manual should prove valuable to persons with diabetes when used in conjunction with a physician's instructions.

Famine, Rationing and Food Policy in Cochin. By K. G. Sivaswamy. With medical surveys by Lt. Col. T. S. Shastry and Dr. J. A. Bhat. 8°, paper, 35 pp., illustrated. Royapettah, Madras: Servindia Kerala Relief Centre, 1946. Rs. 3.

In this pamphlet the economics and control of food in Cochin State are discussed. The author advocates a short-range program to arrest deterioration in the health of children and expectant and nursing mothers. Special attention is called to malnutrition and to inadequate diets. The appendixes are devoted to statistics.

Rare Diseases and Some Debatable Subjects. By F. Parkes Weber, M.D., F.R.C.P., physician to the German Hospital, London. 8°, cloth, 174 pp., illustrated. London: Staples Press, Limited, 1946. 15 sh.

This collection of thirty-one short articles, mostly reprinted from medical periodicals, covers the whole field of clinical medicine. Among the subjects briefly discussed are dysplasias and dystrophies of the subcutaneous tissue, unusual forms of rheumatoid arthritis, vascular disorders, flushing and blushing, calcinosis, endocrinologic conditions, diseases of the liver and biliary ducts and disorders of the nervous system. There are also short chapters on overnutrition, on the influence of Freud, on euthanasia and on the urge to collect. The volume ends with a short series of epigrams and poems.

NOTICES

MASSACHUSETTS CENTRAL HEALTH COUNCIL

The annual luncheon meeting of the Massachusetts Central Health Council will be held on Thursday, May 1, at noon at the Women's Educational and Industrial Union, 264 Boylston Street, Boston. The subject for discussion will be "Local Health Councils." Several active councils will report briefly on their work, after which Dr. Elmer S. Bagnall, former president of the Massachusetts Medical Society, and Dr. Hugh R. Leavell, professor of public-health administration, Harvard School of Public Health, will open the discussion.

Physicians and other persons interested in any aspect of public health are invited to attend. The lunch will cost $1.50. Persons who wish to be present should notify the secretary, Mr. Arthur J. Strawson, 1148 Little Building, Boston (HANcock 5480).

TUBERCULOSIS INSTITUTE

A better understanding of the tuberculous patient, with an emphasis on the psychiatric approach to this problem, will be the topic of an all-day institute to be held on May 9 at the Hotel Bradford, Boston. The program has been arranged particularly by the Massachusetts Conference of Tuberculosis Secretaries, an organization composed of professional workers on the staffs of the Massachusetts Tuberculosis League and its affiliated associations. Several other agencies, including the Massachusetts Medical Society, are also sponsoring the meeting.

The program will include a morning session, a luncheon meeting and a panel discussion in the afternoon. Outstanding authorities in the field of tuberculosis and psychiatry have been invited to participate. Inquiries regarding the institute should be addressed to Miss Mabel M. Brown, Program Committee, Cambridge Tuberculosis and Health Association, 689 Massachusetts Avenue, Cambridge.

PHI DELTA EPSILON LECTURE

The first annual Phi Delta Epsilon Lecture at the Hahnemann Medical College, Philadelphia, will be delivered by Dr. Frank H. Lahey, of Boston, on Monday, May 12. Dr. Lahey will speak on the subject "Surgery of the Stomach, Duodenum and Jejunum."

HARVARD MEDICAL ALUMNI ASSOCIATION

The annual meeting and dinner of the Harvard Medical Alumni Association will be held at the Hotel Claridge, Atlantic City, New Jersey, on Wednesday, June 11, at 7:0 p.m., during the sessions of the one-hundredth-anniversary meeting of the American Medical Association.

TUFTS MEDICAL ALUMNI DINNER

During the celebration of the one hundredth anniversary of the American Medical Association in Atlantic City, th Tufts Medical Alumni Association will hold a dinner o Wednesday, June 11, at 6:30 p.m., at the Ritz-Carlton Hote All alumni and their guests are invited to attend. There wi be speakers from Boston and other cities who will discuss th medical school and its activities.

RESIDENCIES IN PSYCHIATRY

Psychiatric residencies have been established at the Pra Diagnostic Hospital, 30 Bennet Street, Boston, and will b one year in duration. The patients will consist largely o those with neuroses or with emotional or personal complica tions of disease. There will also be a limited number of pa tients with psychosis. The residents' work will consist of th diagnosis and workup of the case and the handling and treat ment of the patient. About 1500 inpatient and 500 out patient cases are seen annually.

Applications will be considered from men of good standin of a Class A medical school who have had either a medica or a neurologic internship as a minimum. Applications shoul be forwarded to Mr. Richard T. Viguers, Administrator.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginnin Thursday, May 1

Thursday, May 1

*12:00 m. Massachusetts Central Health Council. Women's Edu cational and Industrial Union, Boston.

Friday, May 2

*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

Monday, May 5

*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

Tuesday, May 6

*12:15-1:15 p.m. Clinicoroentgenological Conference. Peter Ben Brigham Hospital.

Wednesday, May 7

*11:00 a.m.-12:00 m. Medical Clinic. Amphitheater, Children' Hospital.

*12:00 m. Clinicopathological Conference. (Children's Hospital Amphitheater, Peter Bent Brigham Hospital.

*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Ortho pedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

April 26-May 4. Industrial Health Meetings. Page 456, issue o March 20.

April 28-May 2. American College of Physicians. Page 206, issue o August 8.

May 1. Massachusetts Central Health Council. Notice above.

May 6. Greater Boston Medical Society. Page 610, issue of April 17.

May 8. Cerebral Hemorrhage. Dr. Raymond Adams. Pentucke Association of Physicians. 8:30 p.m. Haverhill.

May 9. Boston University School of Medicine Alumni Association Page 554, issue of April 10.

May 9. Tuberculosis Institute. Notice above.

May 12. Phi Delta Epsilon Lecture. Notice above.

May 19-22. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

May 20-22. Massachusetts Physicians' Art Association. Page 340, issue of February 27.

June 5-8. American College of Chest Physicians. Page 418, issue o March 13.

June 7 and 8. American Society for the Study of Sterility. Page 304 issue of February 20.

(*Notices continued on page xv*)

NOTICES (*Continued from page 646*)

JUNE 9-13. American Medical Association. Page 698, issue of November 7.

JUNE 11. Harvard Medical Alumni Association. Page 646.

JUNE 11. Tufts Medical Alumni Dinner. Page 646.

JUNE 16-18. New England Health Institute. Page 340, issue of February 27.

JUNE 30-JULY 3. American Urological Association. Hotel Statler, Buffalo.

SEPTEMBER 2-6. American Congress of Physical Medicine. Page 610, issue of April 17.

SEPTEMBER 2-7. International Cancer Research Congress. Page 340, issue of February 27.

SEPTEMBER 8-12. Third American Congress on Obstetrics and Gynecology. Page 340, issue of February 27.

OCTOBER 6-10. American Public Health Association. Page 456, issue of March 20.

DISTRICT MEDICAL SOCIETIES

PLYMOUTH

MAY 15. Lakeville Sanatorium, Lakeville.

SUFFOLK

MAY 1. Censors' Meeting.

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The Ophthalmological Study Council

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Westbrook Junior College, Portland, Maine, June 20 to September 13, 1947. All the basic subjects required by the American Board of Ophthalmology. Laboratory work in Pathology and Optics. Practical work in Slit Lamp, Perimetry and Refraction.

Fee: $300; single subjects, $40 a week.

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(Ferrous Sulfate, gr. iv)

are coated twice to provide a doubly protected Ferrous Sulfate offering these therapeutic advantages:

1 **Inner coating prevents premature oxidation in vivo.**

2 **Outer coating increases palatability and aids in preventing tooth discoloration.**

Write Dept. N4 for professional sample.

Kenmore Pharmacy, Inc.
500 Commonwealth Ave.
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FOR THE ALLERGIC PATIENT

AR-EX Cosmetics are the only complete line of *unscented cosmetics* regularly stocked by pharmacies. To be certain that your perfume sensitive patients do not get scented cosmetics, prescribe *AR-EX Unscented Cosmetics*. SEND FOR FREE FORMULARY.

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1000 cc. flasks
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for hospitals.

1 LITER (1000 cc.)
AMIGEN 5%
IN 5% DEXTROSE SOLUTION
A sterilized, aqueous, non-pyrogenic, 5 percent (weight/volume) solution of a pancreatic hydrolysate of casein containing amino acids and polypeptides with 5 percent dextrose. Hydrogen-ion concentration adjusted to pH 6.5.
WARNING. Do not use if the solution is cloudy or if sediment is present. The contents of this bottle must not be used for more than one infusion. For storage, keep the unopened bottle in a cool place.
Use before
Test No.
MEAD JOHNSON & CO.
EVANSVILLE, IND., U.S.A.

COUNCIL-ACCEPTED
AMIGEN
for parenteral administration of amino acids

The function of Amigen and Protolysate is to supply the amino acids essential for nutrition. Both can be given in place of protein when protein cannot be eaten or digested, or in addition to protein when the protein intake is insufficient. Administered in adequate amounts, they prevent wastage of protein, restore previous losses, or build up new body protein.

COUNCIL-ACCEPTED
PROTOLYSATE
for oral and tube feeding of amino acids

PROTOLYSATE
For Oral Administration
A dry enzymic digest of casein containing amino acids and polypeptides, useful as a source of readily absorbed food nitrogen when given orally or by tube. Protolysate is designed for administration in cases requiring predigested protein. The mode of administration and the amount to be given should be prescribed by the physician.
MEAD JOHNSON & CO.
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Like Amigen, Protolysate is an enzymic digest of casein and consists of amino acids and polypeptides. Like Amigen, Protolysate supplies the nitrogen essential for maintenance, repair and growth.

Unlike Amigen, which may be employed both orally and parenterally, Protolysate is designed only for oral use.

1 lb. cans at drug stores

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